

1H), 3.84 (s, 3H), 3.60 (q, 2H,  $J = 7.1$ ), 3.00 (s, 6H), 2.93 (t, 2H,  $J = 7.6$ ), 2.33 (s, 3H); ESI-MS  $m/z$ : 378 (MH<sup>+</sup>).

5     Example 151: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(3,4-DICHLOROPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 140 °C, 6 h), Q (dioxane, 120 °C), and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 (d, 1H,  $J = 2.5$ ), 7.35 - 7.30 (m, 4H), 7.29 - 7.22 (m, 10  
2H), 7.13 (dd, 1H,  $J = 1.5, 8.5$ ), 6.19 (br s, 1H), 5.21 (s, 1H), 3.78 (t, 4H,  $J = 5.0$ ), 3.55 (s, 2H), 3.00 (s, 6H), 2.49 (t, 4H,  $J = 5.0$ ); ESI-MS  $m/z$ : 457 (MH<sup>+</sup> with <sup>35</sup>Cl, <sup>35</sup>Cl), 459 (MH<sup>+</sup> with <sup>35</sup>Cl, <sup>37</sup>Cl), 461 (MH<sup>+</sup> with <sup>37</sup>Cl, <sup>37</sup>Cl).

15

Example 152: N<sup>4</sup>-[4-(BENZYLOXY)CYCLOHEXYL]-2-(4-BENZYL-1-PIPERAZINYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (16 h), Q, and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42 - 7.18 (m, 10H), 4.94 (s, 1H), 4.61 (d, 1H,  $J = 11.8$ ), 4.51 (d, 1H,  $J = 11.8$ ), 4.39 (br s, 1H), 3.75 (t, 4H,  $J = 5.0$ ), 3.53 (s, 2H), 3.31 (dt, 1H,  $J = 5.3, 8.3$ ), 2.95 (s, 6H), 2.46 (t, 4H,  $J = 5.0$ ), 2.19 -

2.11 (m, 1H), 2.07 - 1.98 (m, 1H), 1.79 - 1.56 (m, 3H),  
1.53 - 1.41 (m, 1H), 1.40 - 1.21 (m, 3H); ESI-MS  $m/z$ : 501  
( $MH^+$ ).

5     Example 153: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4,N^4$ -DIMETHYL- $N^6$ -  
[(1R,2R,4R)-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL]-4,6-  
PYRIMIDINEDIAMINE: Prepared by Procedures P (90 °C, 16  
h), Q, and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.44 - 7.22 (m,  
6H), 4.81 (s, 1H), 4.36 (d, 1H,  $J = 7.0$ ), 3.74 (s, 4H),  
10     3.53 (s, 2H), 2.98 (s, 6H), 2.46 (t, 4H,  $J = 5.1$ ), 1.84  
(dd, 1H,  $J = 8.9, 12.9$ ), 1.78 - 1.52 (m, 4H), 1.29 - 1.11  
(m, 2H), 0.97 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H); ESI-MS  
 $m/z$ : 449 ( $MH^+$ ).

15     Example 154:  $N^4,N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-  
(TETRAHYDRO-2-FURANYLMETHYL)-1-PIPERAZINYL]-4,6-  
PYRIMIDINEDIAMINE: Prepared by Procedures A, P (16 h),  
and Q (dioxane, 120 °C).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.17  
(d, 2H,  $J = 8.4$ ), 7.11 (d, 2H,  $J = 8.0$ ), 6.22 (br s, 1H),  
20     5.29 (s, 1H), 4.12 - 4.03 (m, 1H), 3.91 (q, 1H,  $J = 6.7$ ),  
3.80 (t, 4H,  $J = 5.1$ ), 3.76 (q, 1H,  $J = 7.5$ ), 2.98 (s,  
6H), 2.57 (t, 4H,  $J = 5.0$ ), 2.56 - 2.40 (m, 2H), 2.32 (s,

3H), 2.05 - 1.96 (m, 1H), 1.94 - 1.80 (m, 2H), 1.57 - 1.45 (m, 1H); ESI-MS  $m/z$ : 397 ( $MH^+$ ).

5      Example 155: 3-{[2-(4-BENZYL-1-PIPERAZINYL)-6-(DIMETHYLAMINO)-4-PYRIMIDINYL]AMINO}PHENOL: Prepared By  
 Procedures P (Toluene, 120 °C, 40 H), Q (dioxane, 120 °C), AND A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.38 - 7.29 (m, 4H),  
 7.28 - 7.26 (m, 1H), 7.13 (t, 1H,  $J$  = 8.0), 6.84 (t, 1H,  
 10       $J$  = 2.8), 6.80 (ddd, 1H,  $J$  = 0.7, 2.0, 7.9), 6.48 (ddd,  
 1H,  $J$  = 0.7, 2.1, 8.0), 6.32 (br s, 1H), 5.32 (s, 1H),  
 3.79 (t, 4H,  $J$  = 5.0), 3.55 (s, 2H), 3.49 (s, 1H), 2.99  
 (s, 6H), 2.50 (t, 4H,  $J$  = 5.0); ESI-MS  $m/z$ : 405 ( $MH^+$ ).

15      Example 156: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ -(4-FLUOROPHENYL)- $N^6$ , $N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE:  
 Prepared by Procedures P (toluene, sodium tert-butoxide,  
 120 °C, 16 h), Q (dioxane, 120 °C), and A.  $^1H$  NMR (400  
 MHz,  $CDCl_3$ )  $\delta$  7.37 - 7.30 (m, 4H), 7.29 - 7.21 (m, 3H),  
 6.99 (t, 2H,  $J$  = 8.6), 6.14 (br s, 1H), 5.13 (s, 1H),  
 20      3.77 (t, 4H,  $J$  = 4.9), 3.54 (s, 2H), 2.97 (s, 6H), 2.48  
 (t, 4H,  $J$  = 4.9); ESI-MS  $m/z$ : 407 ( $MH^+$ ).

Example 157: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ , $N^4$ -DIMETHYL- $N^6$ -(4-METHYLCYCLOHEXYL)-4,6-PYRIMIDINEDIAMINE: Prepared by

Procedures P (sodium tert-butoxide, toluene, 120 °C, 16 h), Q (dioxane, 120 °C), and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35 - 7.10 (m, 6H), 4.82 (d, 1H, J = 4.9), 3.81 - 3.61 (m, 5H), 3.53 (s, 2H), 2.99 (s, 6H), 2.46 (t, 4H, J = 4.5), 1.79 - 1.46 (m, 7H), 1.29 - 0.98 (m, 2H), 0.90 (d, 3H, J = 6.6); ESI-MS m/z: 409 (MH<sup>+</sup>).

Example 158: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-[4-(DIMETHYLAMINO)PHENYL]-N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (sodium tert-butoxide, toluene, 120 °C, 16 h), Q (neat, 130 °C), and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 - 7.22 (m, 5H), 7.14 (d, 2H, J = 8.4), 6.71 (d, 2H, J = 8.8), 6.04 (br s, 1H), 5.08 (s, 1H), 3.85 - 3.74 (m, 4H), 3.54 (s, 2H), 2.94 (s, 6H), 2.93 (s, 6H), 2.48 (t, 4H, J = 5.1); ESI-MS m/z: 432 (MH<sup>+</sup>).

Example 159: N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-2-[4-(2-PHENYLETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedure S (toluene, 120 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34 - 7.20 (m, 5H), 7.18 (d, 2H, J = 8.5), 7.12 (d, 2H, J = 8.5), 6.21 (br s, 1H), 5.26 (s, 1H),



3.88 - 3.79 (m, 4H), 2.99 (s, 6H), 2.90 - 2.83 (m, 2H),  
 2.68 - 2.63 (m, 2H), 2.60 (t, 4H,  $J = 4.4$ ), 2.32 (s, 3H);  
 ESI-MS  $m/z$ : 417 ( $MH^+$ ).

5     Example 160:     2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ -(3-CHLOROPHENYL)- $N^6,N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, sodium tert-butoxide, 120 °C, 40 h), Q (dioxane, 120 °C), and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.48 (t, 1H,  $J = 1.9$ ), 7.38 - 7.23 (m, 5H),  
 10     7.20 - 7.11 (m, 2H), 6.95 (ddd, 1H,  $J = 1.2, 1.9, 7.6$ ),  
 6.28 (br s, 1H), 5.24 (s, 1H), 3.79 (t, 4H,  $J = 5.0$ ),  
 3.54 (s, 2H), 3.00 (s, 6H), 2.49 (t, 4H,  $J = 5.0$ ); ESI-MS  
 $m/z$ : 423 ( $MH^+$  with  $^{35}Cl$ ), 425 ( $MH^+$  with  $^{37}Cl$ ).

15     Example 161:      $N^2,N^4,N^4$ -TRIMETHYL- $N^6$ -(4-METHYLPHENYL)- $N^2$ -[2-(2-PYRIDINYL)ETHYL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by  
 Procedures F (dioxane, potassium tert-butoxide, 140 °C, 16 h), Q, and A ( $CH_2Cl_2$ ,  $\Delta$ , TEA).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$   
 8.54 (ddd, 1H,  $J = 1.2, 2.1, 5.3$ ), 7.57 (dt, 1H,  $J = 1.7,$   
 20     7.6), 7.23 (d, 2H,  $J = 8.6$ ), 7.18 (d, 1H,  $J = 7.7$ ), 7.14  
 - 7.09 (m, 1H), 7.10 (d, 2H,  $J = 7.7$ ), 6.29 (br s, 1H),  
 5.24 (s, 1H), 3.93 (dd, 2H,  $J = 5.9, 7.8$ ), 3.11 (dd, 2H,

$J = 6.0, 7.7), 3.08 (s, 3H), 3.00 (s, 6H), 2.32 (s, 3H);$   
ESI-MS  $m/z$ : 363 ( $MH^+$ ).

Example 162:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)- $N^2$ -(3-PHENYLPROPYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared using Procedures R, S, and V.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.25 (d, 2H,  $J = 7.7$ ), 7.22 - 7.14 (m, 5H), 7.11 (d, 2H,  $J = 8.1$ ), 6.41 (br s, 1H), 5.27 (s, 1H), 4.76 (t, 1H,  $J = 5.7$ ), 3.41 (dd, 2H,  $J = 7.0, 12.9$ ), 2.96 (s, 6H), 2.70 (t, 2H,  $J = 7.7$ ), 2.31 (s, 3H), 1.91 (t, 2H,  $J = 7.5$ ); ESI-MS  $m/z$ : 362 ( $MH^+$ ).

Example 163: 2-(4-CYCLOHEXYL-1-PIPERAZINYL)- $N^4$ -(3-METHOXYPHENYL)- $N^6, N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared using Procedures P (16 h), Q (dioxane, 120 °C), and A.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.11 (t, 1H,  $J = 8.3$ ), 6.92 (t, 1H,  $J = 2.4$ ), 6.78 - 6.73 (m, 1H), 6.53 - 6.48 (m, 1H), 6.39 (br s, 1H), 5.27 (s, 1H), 3.72 (t, 4H,  $J = 5.0$ ), 3.71 (s, 3H), 2.92 (s, 6H), 2.55 (t, 4H,  $J = 5.1$ ), 2.28 - 2.18 (m, 1H), 1.87 - 1.79 (m, 2H), 1.77 - 1.68 (m, 2H), 1.56 (d, 1H,  $J = 12.4$ ), 1.24 - 1.08 (m, 4H), 1.08 - 0.97 (m, 1H); ESI-MS  $m/z$ : 411 ( $MH^+$ ).

Example 164: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(3-FLUOROPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (140 °C, 4 h), Q (neat, 130 °C),  
 5 and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 - 7.31 (m, 5H), 7.28  
 - 7.17 (m, 2H), 6.98 (ddd, 1H, J = 0.7, 2.0, 8.1), 6.67  
 (ddt, 1H, J = 0.9, 2.0, 8.3), 6.30 (br s, 1H), 5.27 (s,  
 1H), 3.79 (t, 4H, J = 5.1), 3.55 (s, 2H), 3.00 (s, 6H),  
 2.50 (t, 4H, J = 5.0); ESI-MS m/z: 407 (MH<sup>+</sup>).

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Example 165: N<sup>4</sup>-(3-METHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24  
 (dd, 1H, J = 1.2, 5.2), 7.19 (t, 1H, J = 8.1), 6.99 (t,  
 15 1H, J = 2.0), 6.96 - 6.91 (m, 2H), 6.83 (ddd, 1H, J =  
 0.8, 1.7, 7.9), 6.57 (dd, 1H, J = 2.0, 8.2), 6.25 (br s,  
 1H), 5.33 (s, 1H), 3.81 (t, 4H, J = 5.2), 3.78 (s, 3H),  
 3.76 (s, 2H), 2.99 (s, 6H), 2.53 (t, 4H, J = 5.1); ESI-MS  
 m/z: 425 (MH<sup>+</sup>).

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Example 166: 2-[4-(2-METHOXYBENZYL)-1-PIPERAZINYL]-N<sup>4</sup>-(3-METHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T (reduction 3 h).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (dd, 1H,  $J = 1.6, 7.6$ ), 7.23 (dd, 1H,  $J = 1.2, 7.6$ ), 7.19 (t, 1H,  $J = 8.3$ ), 7.01 (t, 1H,  $J = 1.9$ ), 6.95 (dt, 1H,  $J = 1.0, 7.3$ ), 6.87 (dd, 1H,  $J = 1.1, 8.3$ ), 6.82 (ddd, 1H,  $J = 1.0, 2.0, 8.2$ ), 6.57 (ddd, 1H,  $J = 0.7, 2.5, 8.2$ ), 6.26 (br s, 1H), 5.32 (s, 1H), 3.82 (s, 3H), 3.81 (t, 4H,  $J = 5.1$ ), 3.78 (s, 3H), 3.62 (s, 2H), 2.99 (s, 6H), 2.55 (t, 4H,  $J = 5.0$ ); ESI-MS  $m/z$ : 449 ( $\text{MH}^+$ ).

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Example 167: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4, N^4$ -DIMETHYL- $N^6$ -[(1R,2S)-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 120  $^\circ\text{C}$ , 16 h), Q (neat, 130  $^\circ\text{C}$ ), and A.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 - 7.22 (m, 5H), 4.82 (s, 1H), 4.51 (br s, 1H), 3.74 (m, 4H), 3.53 (s, 2H), 2.97 (s, 6H), 2.47 (t, 4H,  $J = 4.7$ ), 2.39 - 2.30 (m, 1H), 1.76 - 1.68 (m, 4H), 1.66 (t, 1H,  $J = 4.7$ ), 1.41 - 1.31 (m, 2H), 0.96 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ESI-MS  $m/z$ : 449 ( $\text{MH}^+$ ).

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Example 168:  $N^4$ -(2-ADAMANTYL)-2-(4-BENZYL-1-PIPERAZINYL)- $N^6, N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE: : Prepared by

Procedures P (90 °C, toluene), Q, and A.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 - 7.21 (m, 5H), 4.83 (s, 1H), 4.72 (br s, 1H), 3.74 (m, 5H), 3.52 (s, 2H), 2.98 (s, 6H), 2.46 (t, 4H,  $J = 5.3$ ), 2.05 - 1.53 (m, 14H); ESI-MS  $m/z$ : 447 ( $\text{MH}^+$ ).

5

Example 169: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ -(4-TERT-BUTYLCYCLOHEXYL)- $N^6$ , $N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 16 h), Q (neat, 130 °C), and A.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 - 7.22 (m, 5H), 4.82 (s, 1H), 3.74 (t, 4H,  $J = 4.7$ ), 3.53 (s, 2H), 3.33 (s, 1H), 2.98 (s, 6H), 2.46 (t, 4H,  $J = 4.7$ ), 1.15 - 0.91 (m, 9H), 0.86 (s, 9H); ESI-MS  $m/z$ : 451 ( $\text{MH}^+$ ).

Example 170: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ -CYCLOOCTYL- $N^6$ , $N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by

Procedures P (16 h), Q, and A.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 - 7.21 (m, 5H), 4.79 (s, 1H), 4.34 (s, 1H), 3.74 (t, 4H,  $J = 4.7$ ), 3.53 (s, 2H), 2.99 (s, 6H), 2.40 (t, 4H,  $J = 4.6$ ), 1.93 - 1.49 (m, 15H); ESI-MS  $m/z$ : 423 ( $\text{MH}^+$ ).

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Example 171: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(4-CHLOROPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (140 °C, Q (neat, 130 °C), and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38 - 7.22 (m, 9H), 6.31 (br s, 1H), 5.21 (s, 1H), 3.78 (t, 4H, J = 5.1 Hz), 3.55 (s, 2H), 2.99 (s, 6H), 2.49 (t, 4H, J = 5.1); ESI-MS m/z: 423 (MH<sup>+</sup> with <sup>35</sup>Cl), 425 (MH<sup>+</sup> with <sup>37</sup>Cl).

Example 172: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(3-CHLORO-4-METHYLPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 120 °C, 16 h), Q (neat, 130 °C), and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.43 - (d, 1H, J = 2.1), 7.38 - 7.09 (m, 5H), 7.07 (d, 1H, J = 2.1), 7.05 (d, 1H, J = 2.6), 6.02 (s, 1H), 5.21 (s, 1H), 3.78 (t, 4H, J = 5.6), 3.54 (s, 2H), 2.99 (s, 6H), 2.49 (t, 4H, J = 5.0), 2.31 (s, 3H); ESI-MS m/z: 437 (MH<sup>+</sup> with <sup>35</sup>Cl), 439 (MH<sup>+</sup> with <sup>37</sup>Cl).

Example 173: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(1,2,3,4-TETRAHYDRO-2-NAPHTHALENYL)-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures P (16 h), Q, and A. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41 - 7.04 (m, 9H), 4.99

(s, 1H), 4.91 (s, 1H), 3.74 (m, 4H), 3.53 (s, 2H), 3.47 (m, 1H), 2.99 (s, 6H), 2.90 - 2.69 (m, 2H), 2.49 (m, 4H), 2.09 - 1.71 (m, 4H); ESI-MS  $m/z$ : 443 ( $MH^+$ ).

5     Example 174:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-(2-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure X ( $NaBH(OAc)_3$ ,  $CH_2Cl_2$ , molecular sieves).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.17 (d, 2H,  $J = 8.3$ ), 7.15 - 7.09 (m, 2H), 7.03 - 6.94 (m, 3H), 5.22 (br s, 1H), 4.85 (s, 1H), 3.86 - 3.79 (m, 4H), 3.77 (s, 2H), 2.98 (s, 6H), 2.62 - 2.53 (m, 4H), 2.32 (s, 3H); ESI-MS  $m/z$ : 409 ( $MH^+$ ).

15     Example 175: 2-[4-(2-METHOXYBENZYL)-1-PIPERAZINYL]- $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure Z.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.40 (dd, 1H,  $J = 1.6, 7.5$ ), 7.23 (dt, 1H,  $J = 1.4, 7.6$ ), 7.17 (d, 2H,  $J = 8.4$ ), 7.10 (d, 2H,  $J = 8.3$ ), 6.94 (t, 1H,  $J = 7.5$ ), 6.87 (d, 1H,  $J = 7.6$ ), 6.17 (br s, 1H), 5.24 (s, 1H), 3.82 (s, 3H), 3.79 (t, 4H,  $J = 5.0$ ), 3.62 (s, 2H), 2.97 (s, 6H), 2.55 (t, 4H,  $J = 5.0$ ), 2.31 (s, 3H); ESI-MS  $m/z$ : 433 ( $MH^+$ ).

Example 176:  $N^2$ -(2-ANILINOETHYL)- $N^4$ , $N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, Q (toluene, 100 °C), and F (potassium *tert*-butoxide, 110 °C, 16 h).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 - 7.10 (m, 6H), 6.67 (dt, 1H,  $J$  = 0.8, 7.3), 6.59 (dd, 2H,  $J$  = 0.8, 8.4), 6.31 (br s, 1H), 5.28 (s, 1H), 4.99 (s, 1H), 3.66 (q, 2H,  $J$  = 6.0), 3.49 (s, 1H), 3.37 (t, 2H,  $J$  = 6.0), 3.00 (s, 6H), 2.33 (s, 3H); ESI-MS  $m/z$ : 363 ( $\text{MH}^+$ ).

Example 177:  $N^4$ -(3-METHOXYPHENYL)- $N^2$ , $N^6$ , $N^6$ -TRIMETHYL- $N^2$ -[2-(2-PYRIDINYL)ETHYL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures F (dioxane, 140 °C, 15 h), A ( $\text{CH}_2\text{Cl}_2$ ,  $\Delta$ , TEA), and Q (toluene, TEA,  $\Delta$ , 40 h).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (d, 1H,  $J$  = 4.7), 7.58 (t, 1H,  $J$  = 7.4), 7.25 - 7.16 (m, 2H), 7.15 - 7.06 (m, 2H), 6.89 (d, 1H,  $J$  = 8.1), 6.57 (d, 1H,  $J$  = 6.7), 6.30 (br s, 1H), 5.31 (s, 1H), 3.95 (t, 2H,  $J$  = 6.4), 3.78 (s, 3H), 3.18 - 3.06 (m, 5H), 3.02 (s, 6H); ESI-MS  $m/z$ : 379 ( $\text{MH}^+$ ).

Example 178:  $N^4$ -(4-CYCLOHEXYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:



Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{Me}_2\text{NH}\text{HCl}$ ,  $-78\text{ }^\circ\text{C}$  for 3.5 h, warmed from  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$  and stirred for 3 h), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.90 (br s, 1H), 8.19-8.16 (m, 1H), 8.09-8.06 (m, 1H), 7.89-7.85 (m, 1H), 7.20-7.18 (m, 4H), 5.28 (s, 1H), 3.99 (t, 4H,  $J = 5.3$ ), 3.73 (t, 4H,  $J = 5.3$ ), 3.04 (s, 6H), 2.53-2.44 (m, 1H), 1.91- 1.71 (m, 4H), 1.46-1.71 (m, 6H); ESI-MS  $m/z$ : 459 ( $\text{MH}^+$ ).

10 Example 179:  $N^4$ -[3-(BENZYLOXY)PHENYL]- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{Me}_2\text{NH}\text{HCl}$ ,  $-78\text{ }^\circ\text{C}$  for 3.5 h, warmed from  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$  and stirred for 3 h), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.82 (br s, 1H), 8.17-8.15 (m, 1H), 8.09-8.06 (m, 1H), 7.89 (d, 1H,  $J = 2.8$ ), 7.45-7.29 (m, 9H), 5.32 (s, 1H), 5.05 (s, 2H), 4.03 (t, 4H,  $J = 5.6$ ), 3.74 (t, 4H,  $J = 5.0$ ), 3.05 (s, 6H); ESI-MS  $m/z$ : 483 ( $\text{MH}^+$ ).

20 Example 180:  $N^4$ -(2,3-DIHYDRO-1H-INDEN-5-YL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,

Me<sub>2</sub>NH<sub>2</sub>Cl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3 h), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.01 (br s, 1H), 8.16 (s, 1H), 8.10-8.97 (m, 1H), 7.91-7.87 (m, 1H), 7.19 (d, 1H, J = 6.3), 7.13 (s, 1H), 7.04 (d, 1H, J = 7.6), 5.23 (s, 1H), 4.03 (t, 4H, J = 5.2), 3.74 (t, 4H, J = 5.1), 3.05 (s, 6H), 2.89 (t, 2H, J = 6.9), 2.14-2.04 (m, 4H); ESI-MS m/z: 417 (MH<sup>+</sup>).

Example 181: N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, Me<sub>2</sub>NH<sub>2</sub>Cl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3 h), N, and O. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.01 (s, 1H), 8.17 (s, 1H), 8.12 - 8.09 (m, 1H), 7.90 (d, 1H, J = 2.6), 7.18 (d, 2H, J = 8.6), 7.16 (d, 2H, J = 8.1), 5.19 (s, 1H), 4.18 - 4.02 (m, 4H), 3.77 (t, 4H, J = 5.1), 3.20 (br s, 3H), 2.99 (br s, 3H), 2.35 (s, 3H); ESI-MS m/z: 391 (MH<sup>+</sup>).

Example 183: N<sup>4</sup>-(3,4-DIMETHYLPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, Me<sub>2</sub>NH<sub>2</sub>Cl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3

h), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.75 (br s, 1H), 8.16 (d, 1H,  $J = 1.3$ ), 8.08 (dd, 1H,  $J = 1.5, 2.8$ ), 7.88 (d, 1H,  $J = 2.5$ ), 7.10 (d, 1H,  $J = 7.8$ ), 7.08 - 7.00 (m, 2H), 5.26 (s, 1H), 4.00 (t, 4H,  $J = 5.1$ ), 3.72 (t, 4H,  $J = 5.0$ ), 3.03 (s, 6H), 2.24 (s, 6H); ESI-MS  $m/z$ : 405 ( $\text{MH}^+$ ).

Example 184: 1-[2-(4-BENZYL-1-PIPERAZINYL)-6-(4-TOLUIDINO)-4-PYRIMIDINYL]-4-PIPERIDINONE: Prepared by Procedures a ( $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 4 H), N (24 H), and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.30 (m, 5H), 7.19-7.10 (m, 4H), 6.24 (s, 1H), 5.40 (s, 1H), 3.84-3.75 (m, 8H), 3.56 (s, 2H), 2.54-2.43 (m, 8H), 2.32 (s, 3H); ESI-MS  $m/z$ : 457 ( $\text{MH}^+$ ).

Example 185:  $N^4, N^4$ -dimethyl- $N^6$ -(2-propylphenyl)-2-[4-(2-pyridinyl)-1-piperazinyl]-4,6-pyrimidinediamine: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , Tea, 3 - 4 H at  $-78^\circ\text{C}$ , then 3 - 4 H at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 - 8.18 (m, 1H), 7.56 - 7.40 (m, 2H), 7.25 - 7.07 (m, 3H), 6.75 - 6.60 (m, 2H), 6.04 (s, 1H), 5.04 (s, 1H), 3.91 (m, 4H), 3.62 (m, 4H), 2.96 (s, 6H), 2.60 (t, 2H,  $J = 7.5$ ), 1.62 (m, 2H), 0.96 (t, 3H,  $J = 8.8$ ); ESI-MS  $M/Z$ : 418 ( $\text{MH}^+$ ).

Example 186:  $N^4$ -(2-BENZYLPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared

by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, AND O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 - 8.18 (M, 1H), 7.54 - 7.45 (M, 1H), 7.34 - 7.04 (M, 9H), 6.73 - 6.59 (M, 2H), 5.99 (BR S, 1H), 5.01 (S, 1H), 3.99 (S, 2H), 3.93 - 3.83 (M, 4H), 3.66 - 3.57 (M, 4H), 2.96 (S, 6H); ESI-MS  $M/Z$ : 466 ( $\text{MH}^+$ ).

Example 187:  $N^4$ -(4-HEXYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 460 ( $\text{MH}^+$ ).

Example 188:  $N^4$ -(4-BENZYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 - 8.18 (m, 1H), 7.52 - 7.45 (m, 1H), 7.32 - 7.09 (m, 9H), 6.78 (d, 1H,  $J = 9.2$ ), 6.65 - 6.59 (m, 1H), 6.24 (br s, 1H), 5.29 (s, 1H), 3.96 (s, 2H), 3.91 - 3.83 (m, 4H), 3.63 - 3.55 (m, 4H), 3.00 (s, 6H); ESI-MS  $m/z$ : 466 ( $\text{MH}^+$ ).

Example 189:  $N^4$ -(4-HEPTYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 -

4 h at 0 °C), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 - 8.18 (m, 1H), 7.57 - 7.44 (m, 1H), 7.38 - 7.08 (m, 4H), 6.75 - 6.57 (m, 2H), 6.26 (br s, 1H), 5.29 (s, 1H), 3.95 - 3.85 (m, 4H), 3.71 - 3.56 (m, 4H), 3.00 (s, 6H), 2.57 (t, 2H,  $J = 5.2$ ), 1.84 - 1.51 (m, 4H), 1.40 - 1.16 (m, 6H), 0.93 - 0.82 (m, 3H); ESI-MS  $m/z$ : 474 ( $\text{MH}^+$ ).

Example 190:  $N^4$ -(3,4-DIMETHYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

10 Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 - 8.19 (m, 1H), 7.55 - 7.44 (m, 1H), 7.31 - 7.23 (m, 1H), 7.14 - 7.02 (m, 2H), 6.73 - 6.59 (m, 2H), 6.18 (br s, 1H), 5.29 (s, 1H), 3.95 - 3.85 (m, 4H), 3.67 - 3.55 (m, 4H), 3.00 (s, 6H), 2.24 (s, 3H), 2.23 (s, 3H), ESI-MS  $m/z$ : 404 ( $\text{MH}^+$ ).

Example 191:  $N^4$ -(3-ISOPROPYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

20 Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 - 8.19 (m, 1H), 7.54 - 7.45 (m, 1H), 7.31 - 7.21 (m,

2H), 7.13 - 7.08 (m, 1H), 6.95 - 6.88 (m, 1H), 6.74 - 6.60 (m, 2H), 6.29 (br s, 1H), 5.37 - 5.34 (m, 1H), 3.96 - 3.87 (m, 4H), 3.68 - 3.57 (m, 4H), 3.00 (s, 6H), 2.95 - 2.85 (m, 1H), 1.36 - 1.19 (m, 6H); ESI-MS  $m/z$ : 418 ( $MH^+$ ).

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Example 192:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-OCTYLPHENYL)-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $CH_2Cl_2$ , TEA, 3 - 4 h at  $-78^\circ C$ , then 3 - 4 h at  $0^\circ C$ ), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.22 (s, 1H), 7.55 - 7.44 (m, 1H), 7.37 - 7.07 (m, 4H), 6.76 - 6.59 (m, 2H), 6.28 (br s, 1H), 5.29 (s, 1H), 3.96 - 3.86 (m, 4H), 3.69 - 3.56 (m, 4H), 3.00 (s, 6H), 2.57 (t, 2H,  $J = 5.1$ ), 1.74 - 1.51 (m, 4H), 1.41 - 1.08 (m, 8H), 0.93 - 0.82 (m, 3H); ESI-MS  $m/z$ : 488 ( $MH^+$ ).

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Example 193:  $N^4$ -(3-IODOPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $CH_2Cl_2$ , TEA, 3 - 4 h at  $-78^\circ C$ , then 3 - 4 h at  $0^\circ C$ ), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.29 - 8.18 (m, 1H), 8.01 - 7.93 (m, 1H), 7.56 - 7.45 (m, 1H), 7.39 - 7.29 (m, 1H), 7.11 - 6.95 (m, 2H), 6.78 - 6.56 (m, 2H), 6.42 - 6.25 (m, 1H), 5.34 (s, 1H), 3.95 - 3.85

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(m, 4H), 3.65 - 3.56 (m, 4H), 3.00 (s, 6H); ESI-MS  $m/z$ : 502 ( $MH^+$ ).

Example 194:  $N^4$ -(4-CHLOROPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared  
 5 by Procedures A ( $CH_2Cl_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ C$ , then 3 - 4 h at  $0\text{ }^\circ C$ ), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.28 (s, 1H), 7.53 - 7.42 (m, 1H), 7.35 - 7.24 (m, 2H), 7.11 - 6.95 (m, 2H), 6.76 - 6.57 (m, 2H), 6.21 (s, 1H), 5.29 (s,  
 10 1H), 3.97 - 3.86 (m, 4H), 3.67 - 3.57 (m, 4H), 3.00 (s, 6H); ESI-MS  $m/z$ : 410 ( $MH^+$ ).

Example 195:  $N^5$ -(2-CHLOROPHENYL)- $N^4,N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,5-PYRIMIDINEDIAMINE: Prepared  
 15 by Procedures A ( $CH_2Cl_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ C$ , then 3 - 4 h at  $0\text{ }^\circ C$ ), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.50 - 8.10 (m, 2H), 7.55 - 7.12 (m, 4H), 7.05 - 6.90 (m, 2H), 6.61 (s, 1H), 5.31 (s, 1H), 3.95-3.85 (m, 4H), 3.65 - 3.54 (m, 4H), 3.00 (s, 6H); ESI-MS  $m/z$ : 410 ( $MH^+$ ).

Example 196:  $N^4$ -(3,4-DIFLUOROPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$   
 5 8.31 (s, 1H), 7.59 - 6.95 (m, 4H), 6.68 - 6.54 (m, 2H),  
 6.29 (s, 1H), 5.27 (s, 1H), 3.94 - 3.82 (m, 4H), 3.63 -  
 3.51 (m, 4H), 3.01 (s, 6H); ESI-MS  $m/z$ : 412 ( $\text{MH}^+$ ).

Example 197:  $N^4$ -[3-METHOXY-5-(TRIFLUOROMETHYL)PHENYL]- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA,  
 10 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR  
 (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 - 8.18 (m, 1H), 7.58 - 7.11 (m,  
 3H), 6.77 - 6.38 (m, 3H), 6.34 (s, 1H), 5.25 (s, 1H),  
 15 3.96 - 3.88 (m, 4H), 3.85 (s, 3H), 3.69 - 3.55 (m, 4H),  
 3.00 (s, 6H); ESI-MS  $m/z$ : 474 ( $\text{MH}^+$ ).

Example 198:  $N^4,N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]- $N^6$ -(2,3,4-TRIFLUOROPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA,  
 20 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR  
 (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 - 8.18 (m, 1H), 7.58 - 7.11 (m,



3H), 6.77 - 6.38 (m, 2H), 6.34 (s, 1H), 5.25 (s, 1H),  
3.96 - 3.88 (m, 4H), 3.85 (s, 3H), 3.69 - 3.55 (m, 4H),  
3.00 (s, 6H); ESI-MS  $m/z$ : 430 ( $MH^+$ ).

5     Example 199:  $N^4$ -(4-BROMO-2-FLUOROPHENYL)- $N^6,N^6$ -DIMETHYL-  
2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $CH_2Cl_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ C$ ,  
then 3 - 4 h at  $0\text{ }^\circ C$ ), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$   
8.27 - 8.17 (m, 1H), 7.61 - 7.01 (m, 4H), 6.75 - 6.57 (m,  
10     2H), 6.34 (br s, 1H), 5.23 (s, 1H), 3.95 - 3.85 (m, 4H),  
3.68 - 3.59 (m, 4H), 3.00 (s, 6H); ESI-MS  $m/z$ : 472 ( $MH^+$ ).

Example 200:  $N^4$ -(4-FLUORO-3-METHYLPHENYL)- $N^6,N^6$ -DIMETHYL-  
2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

15     Prepared by Procedures A ( $CH_2Cl_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ C$ ,  
then 3 - 4 h at  $0\text{ }^\circ C$ ), N, and O.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$   
8.27 - 8.17 (m, 1H), 7.56 - 7.47 (m, 1H), 7.21 - 6.89 (m,  
3H), 6.75 - 6.58 (m, 2H), 6.24 (br s, 1H), 5.18 (s, 1H),  
3.95 - 3.84 (m, 4H), 3.69 - 3.55 (m, 4H), 3.00 (s, 6H),  
20     2.25 (s, 3H); ESI-MS  $m/z$ : 408 ( $MH^+$ ).

Example 201:  $N^4$ -(2,5-DIMETHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ\text{C}$ , then 3 - 4 h at  $0\text{ }^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$   
 5 8.27 - 8.16 (m, 1H), 7.96 - 7.86 (m, 1H), 7.56 - 7.43 (m, 1H), 6.93 - 6.42 (m, 5H), 5.31 (s, 1H), 4.01 - 3.90 (m, 4H), 3.84 (s, 3H), 3.79 (s, 3H), 3.70 - 3.54 (m, 4H), 3.04 (s, 6H); ESI-MS  $m/z$ : 436 ( $\text{MH}^+$ ).

10 Example 202:  $N^4$ -(3,5-DIMETHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ\text{C}$ , then 3 - 4 h at  $0\text{ }^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$   
 15 8.26 - 8.17 (m, 1H), 7.55 - 7.44 (m, 1H), 6.73 - 6.58 (m, 2H), 6.59 - 6.53 (m, 2H), 6.23 (br s, 1H) 5.37 (s, 1H), 3.98 - 3.88 (m, 4H), 3.77 (s, 6H), 3.62 - 3.58 (m, 4H), 3.01 (s, 6H); ESI-MS  $m/z$ : 436 ( $\text{MH}^+$ ).

20 Example 203:  $N^4$ -[3-(BENZYLOXY)PHENYL]-2-[4-(3-BROMOPHENYL)-1-PIPERAZINYL]- $N^6,N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78\text{ }^\circ\text{C}$ , then 3 - 4 h at  $0\text{ }^\circ\text{C}$ ), N (TEA), and O.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 - 6.26 (m, 14H), 5.29 (s, 1H), 5.06 (s, 2H), 3.97 - 3.82 (m, 4H), 3.21 - 3.14 (m, 4H), 3.01 (s, 6H); ESI-MS  $m/z$ : 560 ( $\text{MH}^+$ ).

5     Example 204:  $N^4$ -(2-BROMO-4-METHYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 - 8.16 (m, 1H), 7.81 (d, 1H,  $J = 8.8$ ), 7.52 - 7.44 (m, 1H), 7.38 (d, 1H,  $J = 8.5$ ), 7.08 (d, 1H,  $J = 8.5$ ), 6.72 (m, 2H), 6.47 (br s, 1H), 5.24 (s, 1H), 3.90 (t, 4H,  $J = 6.3$ ), 3.61 (t, 4H,  $J = 6.4$ ), 3.01 (s, 6H), 2.28 (s, 3H); ESI-MS  $m/z$ : 468 ( $\text{MH}^+$ ).

15     Example 205:  $N^4$ -(2,4-DICHLOROPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 - 8.17 (m, 1H), 8.21 (d, 1H,  $J = 9.2$ ), 7.49 (t, 1H,  $J = 9.0$ ), 7.38 - 7.16 (m, 2H), 6.71 - 6.59 (m, 2H), 6.57 (br s, 1H), 5.25 (s, 1H), 3.93 - 3.85 (m, 4H), 3.65 - 3.55 (m, 4H), 3.03 (s, 6H); ESI-MS  $m/z$ : 444 ( $\text{MH}^+$ ).

Example 206:  $N^4$ -(3-FLUOROPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 - 6.39 (m, 9H), 5.30 (s, 1H), 3.97 - 3.85 (m, 4H), 3.74 - 3.58 (m, 4H), 3.01 (s, 6H); ESI-MS  $m/z$ : 394 ( $\text{MH}^+$ ).

Example 207:  $N^4,N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]- $N^6$ -[3-(TRIFLUOROMETHOXY)PHENYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 460 ( $\text{MH}^+$ ).

15

Example 208:  $N^4$ -(2,5-DICHLOROPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 445 ( $\text{MH}^+$ ).

20

Example 209:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-PROPYLPHENYL)-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 418 ( $\text{MH}^+$ ).

5

Example 210:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-PENTYLPHENYL)-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 446 ( $\text{MH}^+$ ).

10

Example 211:  $N^4$ -(4-SEC-BUTYLPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 432 ( $\text{MH}^+$ ).

15

Example 212:  $N^4$ -(2-TERT-BUTYLPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 432 ( $\text{MH}^+$ ).

20

Example 213:  $N^4$ -(2,5-DIMETHYLPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 404 ( $\text{MH}^+$ ).

5

Example 214:  $N^4$ -(3,5-DIMETHYLPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 404 ( $\text{MH}^+$ ).

10

Example 215:  $N^4$ -(2,3-DIMETHYLPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 404 ( $\text{MH}^+$ ).

15

Example 216:  $N^4$ -(3-BENZYLPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 466 ( $\text{MH}^+$ ).

20

Example 217:  $N^4$ -(4-BROMO-2-CHLOROPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 489 ( $\text{MH}^+$ ).

5

Example 218:  $N^4$ -(2,3-DICHLOROPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 445 ( $\text{MH}^+$ ).

10

Example 219:  $N^4$ , $N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]- $N^6$ -(2,4,5-TRIFLUOROPHENYL)-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 430 ( $\text{MH}^+$ ).

15

Example 220:  $N^4$ -(5-CHLORO-2-METHOXYPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 440 ( $\text{MH}^+$ ).

20

Example 221:  $N^4, N^4$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]- $N^6$ -(3,4,5-TRIFLUOROPHENYL)-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 430 ( $\text{MH}^+$ ).

Example 222:  $N^4$ -(2-CHLORO-5-FLUOROPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 428 ( $\text{MH}^+$ ).

Example 223:  $N^4$ -(2-CHLORO-4-METHYLPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 424 ( $\text{MH}^+$ ).

Example 224:  $N^4$ -(3-CHLOROPHENYL)- $N^6, N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared

by Procedures A ( $\text{CH}_2\text{Cl}_2$ , TEA, 3 - 4 h at  $-78^\circ\text{C}$ , then 3 - 4 h at  $0^\circ\text{C}$ ), N, and O. ESI-MS  $m/z$ : 410 ( $\text{MH}^+$ ).



Example 225: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-[3-METHOXY-5-(TRIFLUOROMETHYL) PHENYL]-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures O (toluene, 75 °C), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 487 (MH<sup>+</sup>).

5

Example 226: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-[2-METHOXY-5-(TRIFLUOROMETHYL) PHENYL]-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures O, Q (dioxane, 120 °C), and A. ESI-MS *m/z*: 487 (MH<sup>+</sup>).

10

Example 227: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(2,5-DIMETHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures O, Q (dioxane, 120 °C), and A. ESI-MS *m/z*: 449 (MH<sup>+</sup>).

15

Example 228: N<sup>4</sup>-[3-(BENZYLOXY) PHENYL]-2-(4-BENZYL-1-PIPERAZINYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures O, Q (toluene, 120 °C), and A. ESI-MS *m/z*: 495 (MH<sup>+</sup>).

20

Example 229: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-[4-(TRIFLUOROMETHYL)PHENYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 105 °C), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 457 (MH<sup>+</sup>).

5 Example 230: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(2,3,4-TRICHLOROPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures O (60 °C), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 492 (MH<sup>+</sup>).

10 Example 231: 2-[4-(2-FURYL METHYL)-1-PIPERAZINYL]-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures R (16 h), P (sodium *tert*-butoxide, toluene, 120 °C), N (TEA, toluene reflux), and A. ESI-MS  $m/z$ : 393 (MH<sup>+</sup>).

15

Example 232: N<sup>2</sup>-[2-(4-METHOXYPHENYL)ETHYL]-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedures V, R, and S (DIEA, DMAP). ESI-MS  $m/z$ : 378 (MH<sup>+</sup>).

20

Example 233:  $N^4$ -(3-METHOXYPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(TETRAHYDRO-2-FURANYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, P (16 h), and Q (dioxane, 120 °C). ESI-MS  $m/z$ : 413 ( $MH^+$ ).

5

Example 235: 2-[4-(4-METHOXYBENZYL)-1-PIPERAZINYL]- $N^4$ , $N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:  
Prepared by Procedure Z. ESI-MS  $m/z$ : 433 ( $MH^+$ ).

10 Example 237:  $N^4$ , $N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)- $N^2$ -[2-(2-THIENYL)ETHYL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures R, S, and V. ESI-MS  $m/z$ : 354 ( $MH^+$ ).

15 Example 238:  $N^4$ , $N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)-2-[4-(3-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:  
Prepared by Procedures AA, T (2 h), and W. ESI-MS  $m/z$ : 409 ( $MH^+$ ).

20 Example 239: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ -[4-CHLORO-2-(TRIFLUOROMETHYL)PHENYL]- $N^6$ , $N^6$ -DIMETHYL-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures O (100 °C, 40 h), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 491 ( $MH^+$ ).

5 Example 240:  $N^4$ -(3-BROMO-4-METHYLPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:  
Prepared by Procedures O (80 °C), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 469 ( $MH^+$ ).

10 Example 241: 2-{4-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}NICOTINONITRILE: Prepared by Procedures O, Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 415 ( $MH^+$ ).

15 Example 242:  $N^4$ , $N^4$ -DIMETHYL- $N^6$ -[4-METHYL-3-(2-PYRIDINYLAMINO)PHENYL]-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 482 ( $MH^+$ ).

20 Example 243:  $N^4$ -(3-BROMOPHENYL)- $N^6$ , $N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared

by Procedures O (85 °C), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 455 ( $MH^+$ ).

5 Example 244: 2-(4-BENZYL-1-PIPERAZINYL)- $N^4$ -[2-CHLORO-4-(TRIFLUOROMETHYL) PHENYL]- $N^6,N^6$ -DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (16 h, toluene), Q (toluene, 120 °C), and A. ESI-MS  $m/z$ : 491 ( $MH^+$ ).

10 Example 245:  $N^4$ -(3-METHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, N, and P. ESI-MS  $m/z$ : 406 ( $MH^+$ ).

15 Example 246:  $N^4$ -(3-METHOXYPHENYL)- $N^6,N^6$ -DIMETHYL-2-{4-[2-(TRIFLUOROMETHYL) PHENYL]-1-PIPERAZINYL}-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, N, and P. ESI-MS  $m/z$ : 473 ( $MH^+$ ).

20 Example 247:  $N^4$ -(3-METHOXYPHENYL)- $N^6,N^6$ -DIMETHYL- $N^2$ -(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, N, and P. ESI-MS  $m/z$ : 364 ( $MH^+$ ).

Example 248:  $N^2, N^4, N^6$ -TRIMETHYL- $N^6$ -(4-METHYLPHENYL)- $N^2$ -(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, N, and P. ESI-MS  $m/z$ : 362 ( $MH^+$ ).

5

Example 249:  $N$ -(4-METHYLPHENYL)-2-{4-[1-OXIDO-3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedure CC. ESI-MS  $m/z$ : 514 ( $MH^+$ ).

10

Example 250:  $N^4, N^4$ -DIMETHYL- $N^6$ -(4-METHYLPHENYL)- $N^2$ -(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures R and S. ESI-MS  $m/z$ : 348 ( $MH^+$ ).

15

Example 251:  $N^4$ -(3-METHOXYPHENYL)- $N^2, N^6, N^6$ -TRIMETHYL- $N^2$ -(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: : Prepared by Procedures A, N, and P. ESI-MS  $m/z$ : 378 ( $MH^+$ ).

Example 252: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>-(3-METHOXYPHENYL)-N<sup>6</sup>,N<sup>6</sup>-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A, N, and P. ESI-MS *m/z*: 419 (MH<sup>+</sup>).

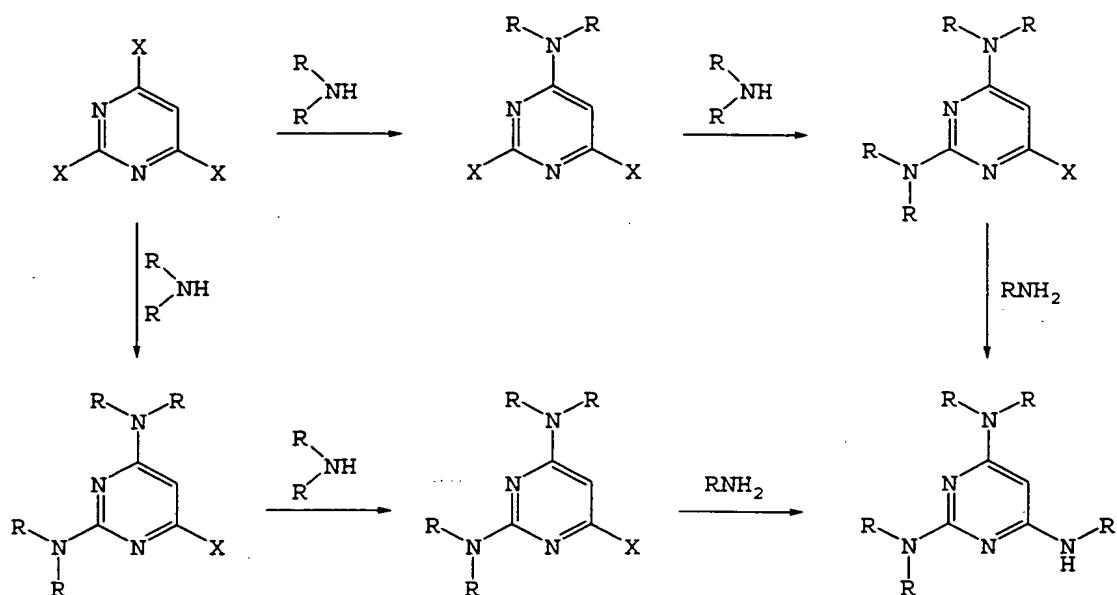
5      Example 253: 2-(4-BENZYL-1-PIPERAZINYL)-N<sup>4</sup>,N<sup>4</sup>-DIMETHYL-N<sup>6</sup>-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:      Prepared by  
Procedures A, N, and P. ESI-MS *m/z*: 403 (MH<sup>+</sup>).

10      Examples 1-90 and 115-253 as described above are merely illustrative of the methods used to synthesize pyrimidine derivatives. Further derivatives may be obtained utilizing methods shown in Schemes 1-5b. The substituents in Schemes 1-5b are described in the Detailed Description.

15      It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form pyrimidine  
20      derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

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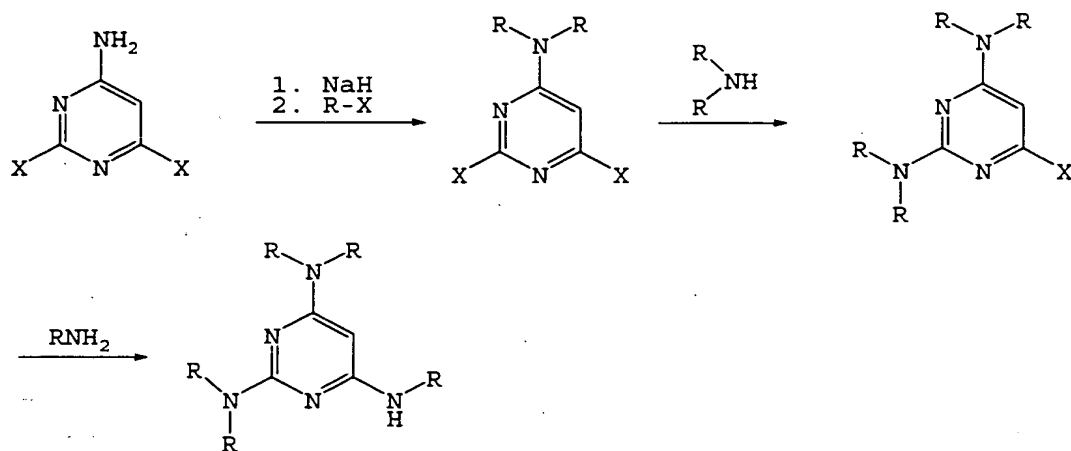
**Scheme 1. Synthesis of Substituted Triaminopyrimidines**



X =leaving group such as halogen  
OTf or OTs

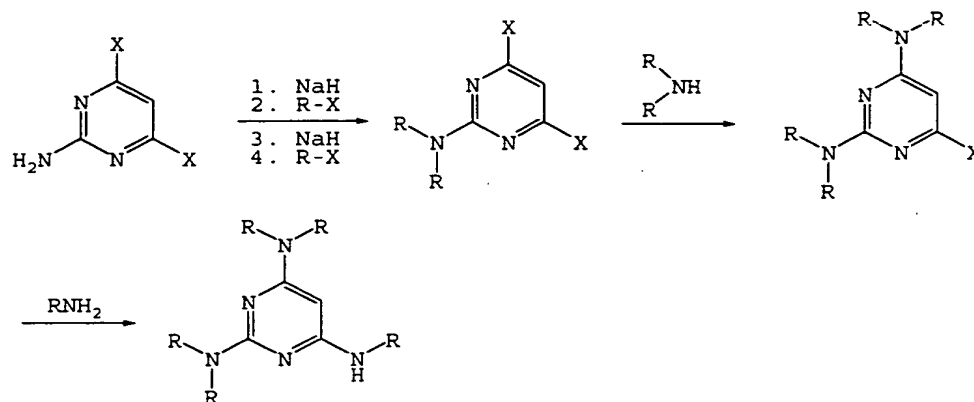


**Scheme 2. Alternate Synthesis of Substituted Triaminopyrimidines**



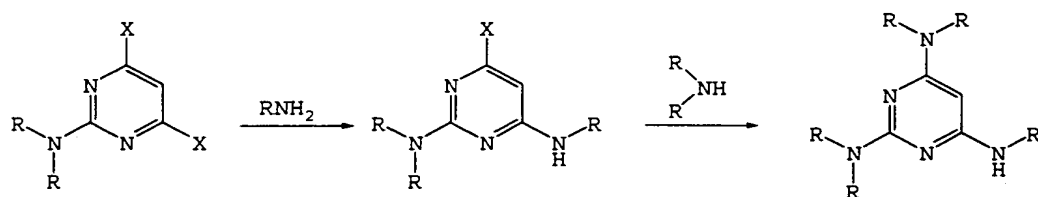
X = leaving group such as halogen  
OTf or OTs

Scheme 3. Alternate Synthesis of Substituted Triaminopyrimidines

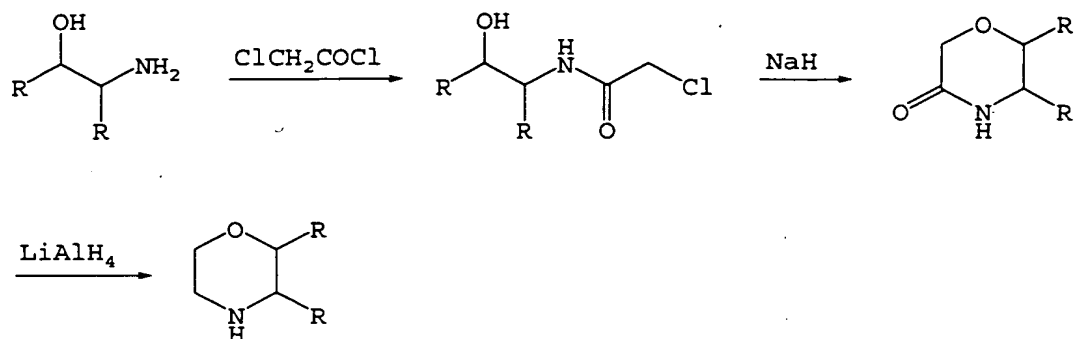


X = leaving group such as halogen  
OTf or OTs

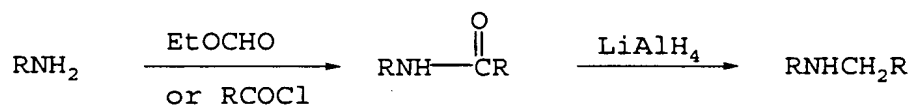
Alternatively,



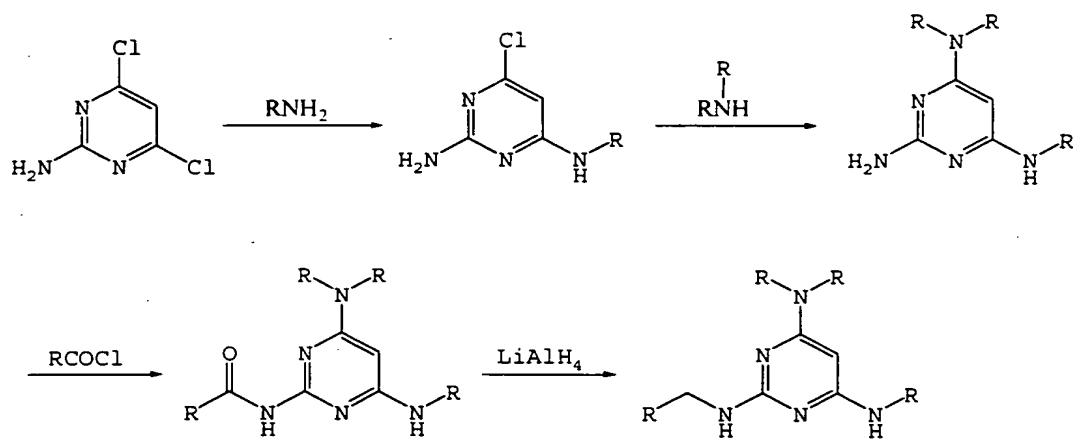
## Scheme 4. Synthesis of Morpholine Intermediates



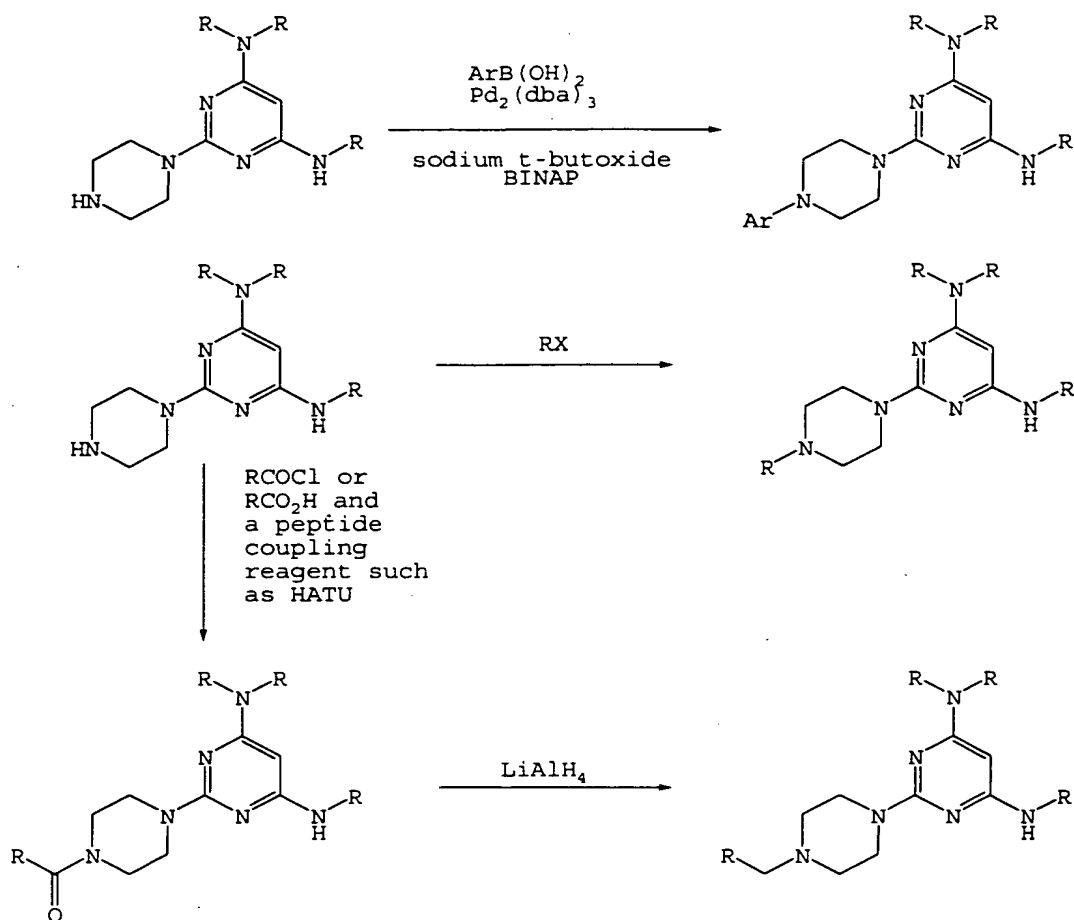
## Scheme 5. Synthesis of N-Alkylamine Intermediates



**Scheme 5a. Synthesis of Triaminopyrimidines from 2-Amidopyrimidines**



**Scheme 5b. Substitution on the Piperazine Moiety of 2-(Piperazin-1-yl)pyrimidines**



X is a leaving group such as a halogen or tosylate; HATU is O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; dba is dibenzylideneacetone; BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

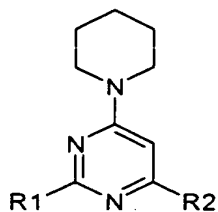
Radioligand Binding of Pyrimidines at Cloned Galanin Receptors

5 The binding properties of the pyrimidines of the present invention were evaluated at the cloned human galanin receptors, GAL1, GAL2, and GAL3, using protocols described herein.

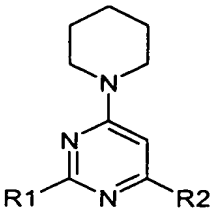
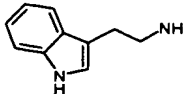
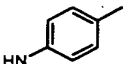
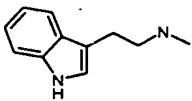
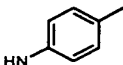
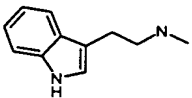
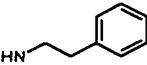
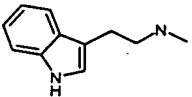
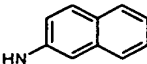
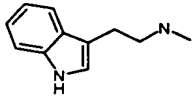
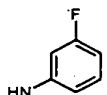
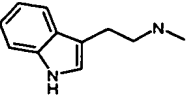
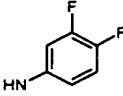
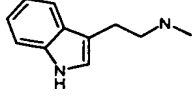
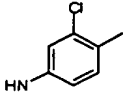
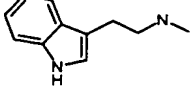
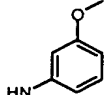
Radioligand Binding Assay Results

10 The pyrimidines described in Examples 1-90 and 115-253 were assayed using cloned human galanin receptors. The compounds were found to be selective for the GAL3 receptor. The binding affinities of the compounds of Examples 1-90 and 115-253 are illustrated in Tables 1-3a.

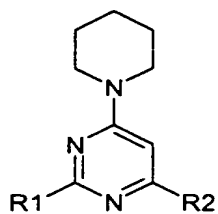
TABLE 1



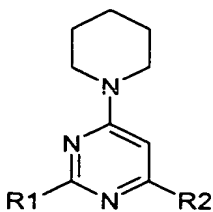
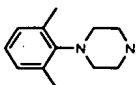
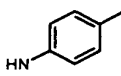
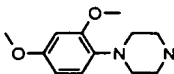
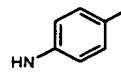
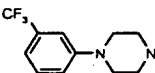
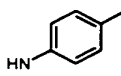
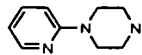
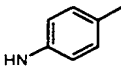
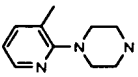
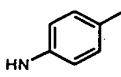
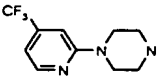
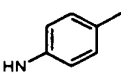
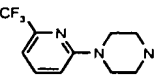
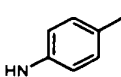
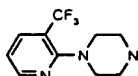
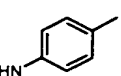
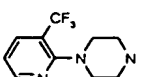

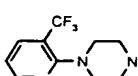

Example	substitution		K <sub>i</sub> (nM)		
	R <sub>1</sub>	R <sub>2</sub>	GalR1	GalR2	GalR3
1			668	188	35
2			2818	562	26
3			>5000	>5000	163
4			>5000	>5000	627
5			>5000	>5000	345
6			>5000	2157	248
7			1107	775	177
8			>5000	795	264
9			>5000	2110	568

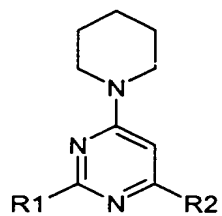
			Table 1 continued		
	substitution			Ki (nM)	
Example	R1	R2	GalR1	GalR2	GalR3
10			>5000	865	100
11			>5000	681	91
12			>5000	1995	322
13			2065	1413	81
14			>5000	1336	54
15			2427	624	73
16			>5000	>5000	33
17			>5000	2089	87



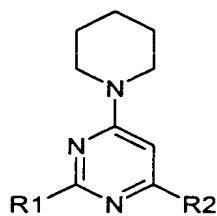
Table 1  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
18			3589	543	40
19			>5000	1771	79
20			>5000	>5000	164
21			4786	1096	49
22			442	176	28
23			>5000	>5000	60
24			>5000	3961	210
25			>5000	1497	548
26			>5000	4049	85

			Table 1 continued		
	substitution			Ki (nM)	
Example	R1	R2	GalR1	GalR2	GalR3
27			2692	272	63
28			>5000	>5000	270
29			716	359	46
30			>5000	2613	197
31			>5000	3402	174
32			>5000	1860	145
33			>5000	>5000	181
34			912	168	23
35					111
36			442	90	93

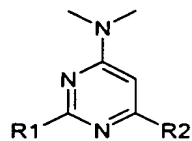
Table 1  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
37			>5000	903	343
38			2901	516	320
39			>5000	>5000	128
40			>5000	2623	164
41			2131	840	151
42			>5000	1137	275
43			>5000	>5000	107
44			>5000	1023	133
45			>5000	>5000	505

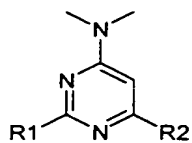
Table 1  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
46			>5000	>5000	577
47			>5000	3012	115
48			>5000	4233	120
49			>5000	3273	211

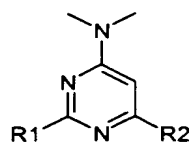
TABLE 2



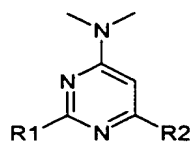
Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
50			>5000	>5000	699
51			>5000	>5000	987
52			>5000	>5000	570
53			>5000	>5000	980
54			>5000	>5000	132
55			>5000	>5000	48
56			>5000	>5000	794
57			>5000	>5000	360
58			>5000	>5000	783
59			>5000	>5000	566
60			>5000	>5000	86

Table 2  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
61			>5000	>5000	753
62			>5000	>5000	736
63			>5000	>5000	731
64			>5000	>5000	572
65			>5000	>5000	329
66			>5000	>5000	699
67			>5000	>5000	752
68			>5000	2155	164
69			>5000	>5000	417
70			>5000	944	476

Table 2  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
71			>5000	944	72
72			>5000	2083	132
73			>5000	1550	124
74			2291	468	47
75			1462	2458	144
76			3802	1657	392
77			3802	709	79
78			4942	1862	41

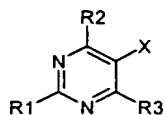
Table 2  
continued

Example	substitution		Ki (nM)		
	R1	R2	GalR1	GalR2	GalR3
79			3802	1656	190
80			>5000	2478	615
81			>5000	4789	160
82			>5000	>5000	232
83			>5000	>5000	160
84			>5000	>5000	261
85			>5000	4228	72
86			>5000	>5000	227
87			>5000	4617	157
88			2188	355	39

Key: Ph = Phenyl



TABLE 3



Example	substitution				Ki (nM)		
	X	R1	R2	R3	GalR1	GalR2	GalR3
89	H				1122	1274	105
90	H				>5000	2460	105

Table 3a.

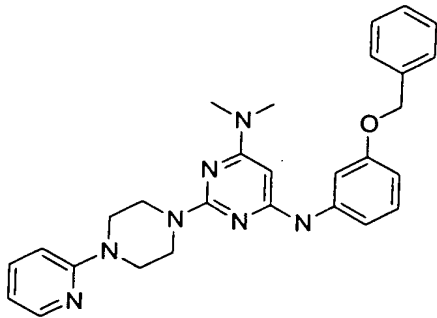
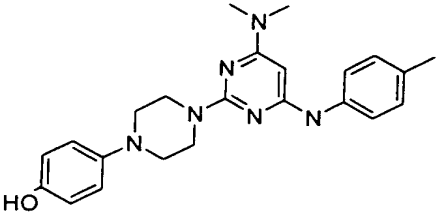
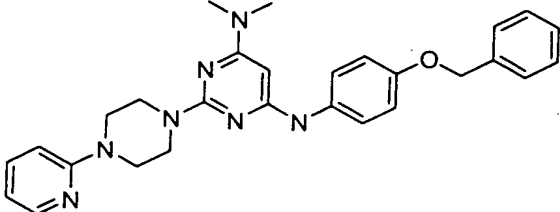
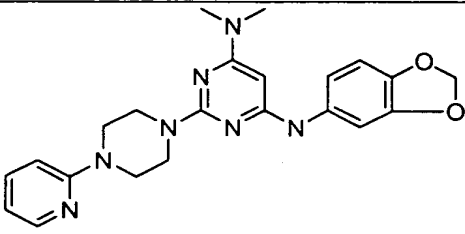
Example	Structure	Ki (nM) Gal3
115		13
116		479
117		61
118		508

Table 3a.

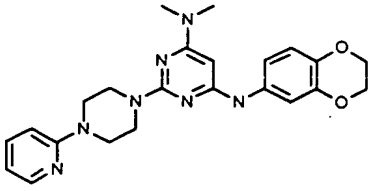
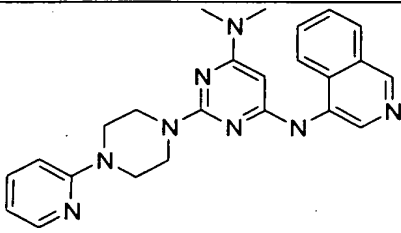
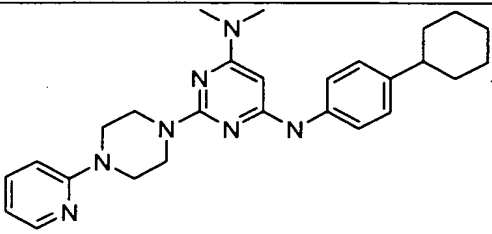
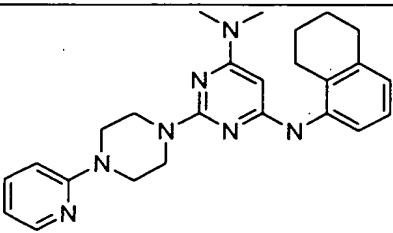
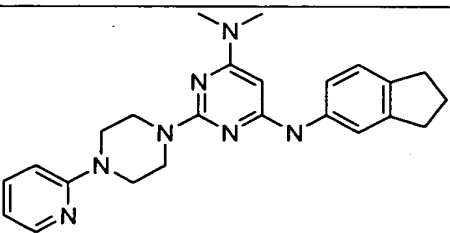
119		540
120		664
121		21
122		65
123		61

Table 3a.

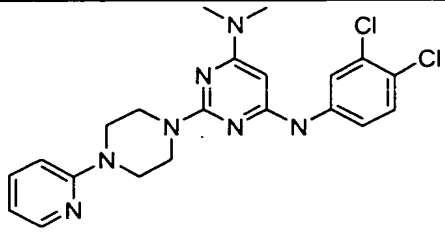
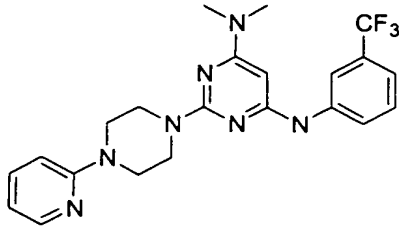
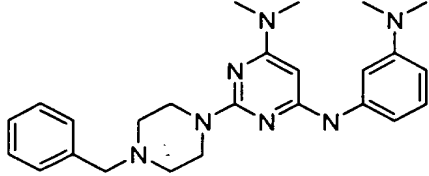
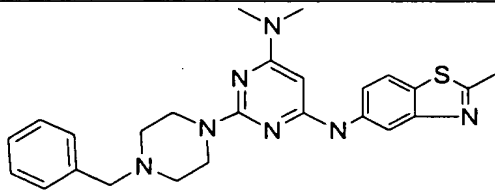
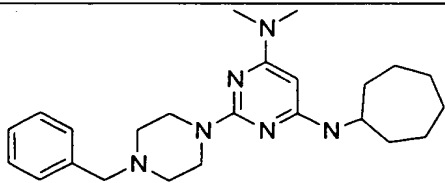
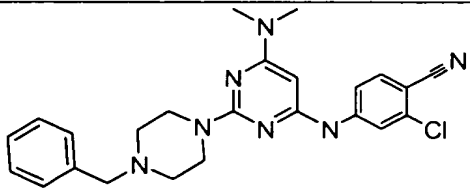
124		36
125		75
126		99
127		255
128		249
129		405

Table 3a.

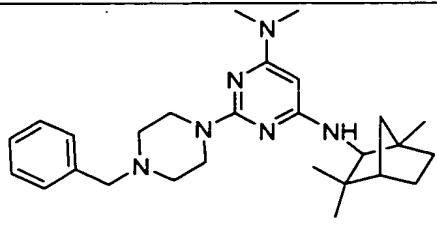
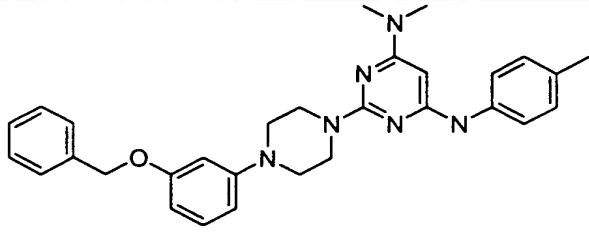
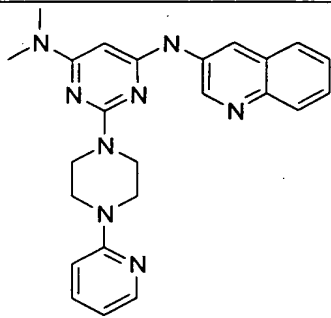
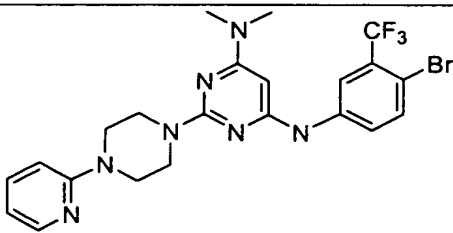
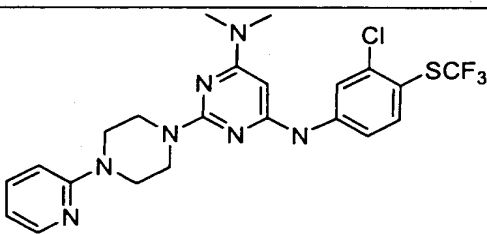
130		100
131		20
132		618
133		60
134		25

Table 3a.

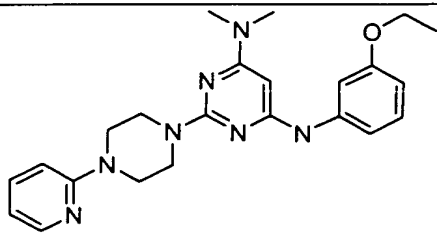
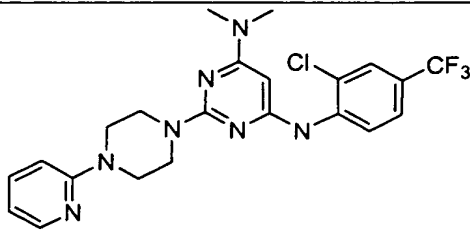
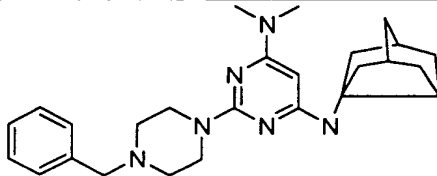
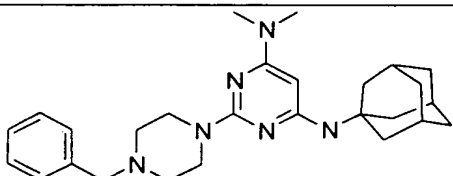
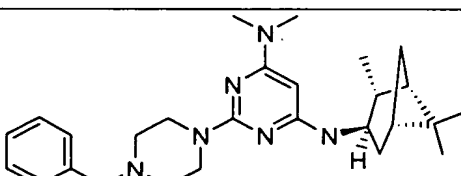
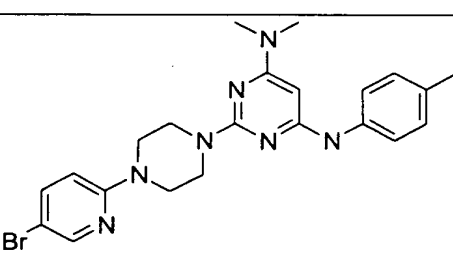
135		100
136		25
137		124
138		52
139		47
140		169

Table 3a.

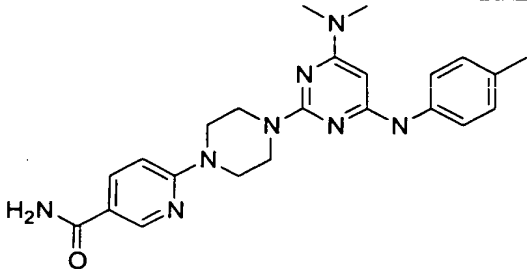
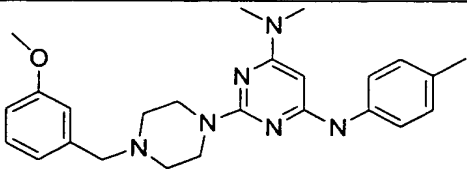
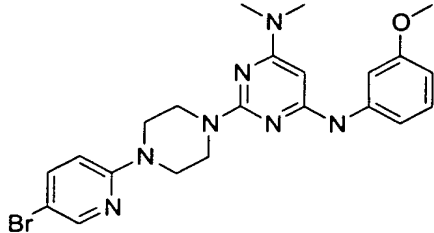
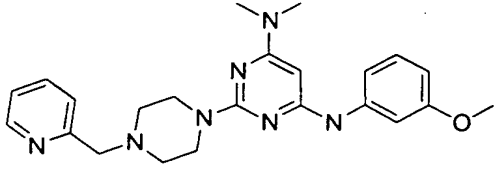
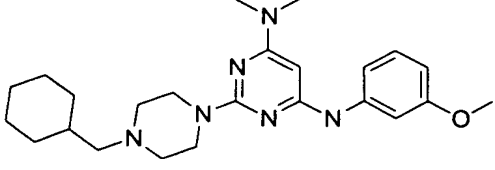
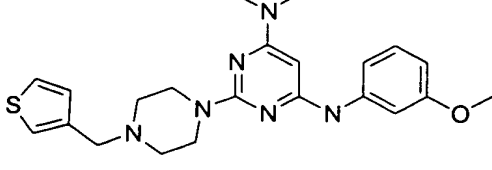
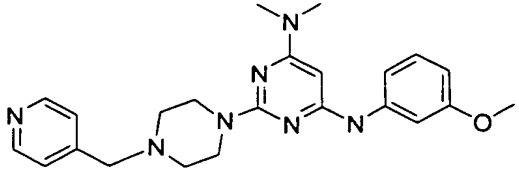
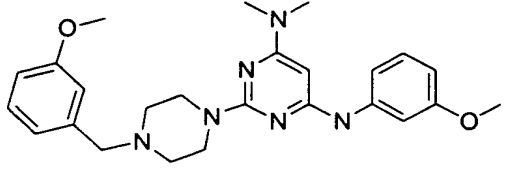
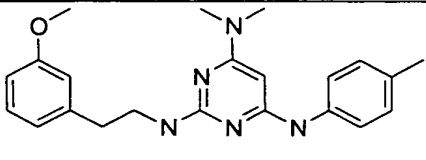
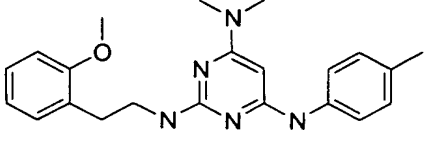
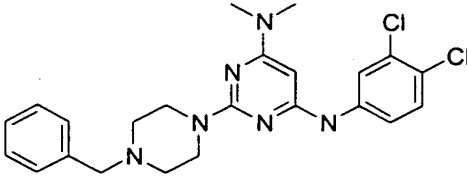
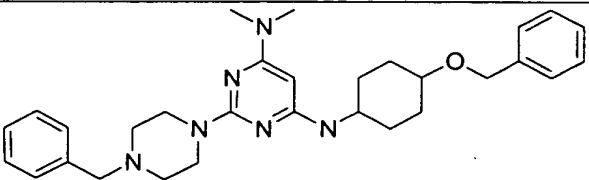
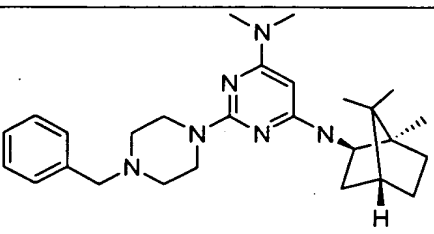
141		509
142		28
143		144
144		529
145		155
146		72

Table 3a.

147		640
148		276
149		138*
150		180
151		11
152		172
153		55

\* The binding assay normally used for the indolone compounds was used to test this compound.



Table 3a.

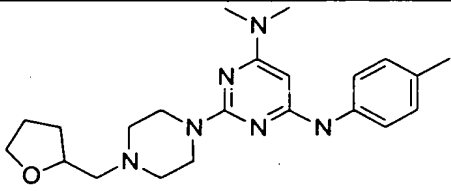
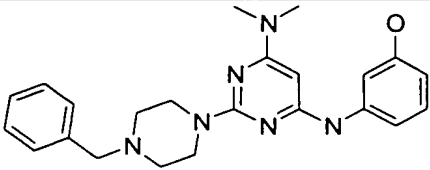
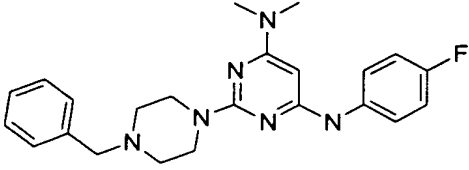
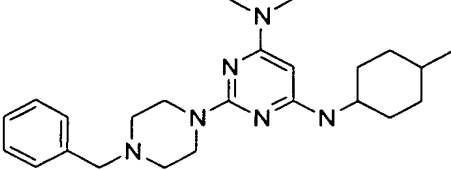
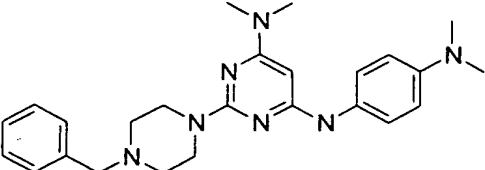
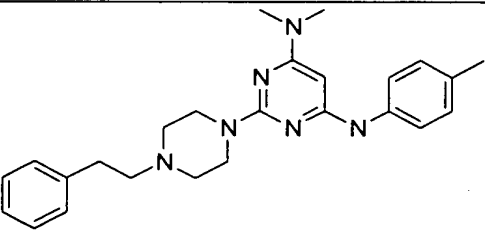
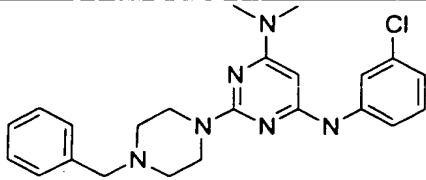
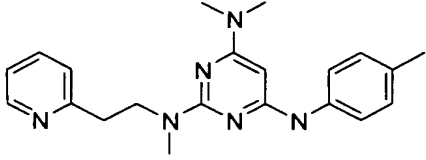
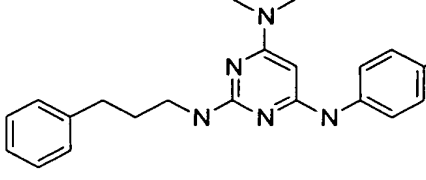
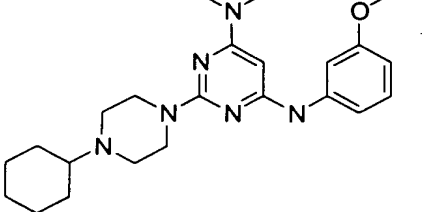
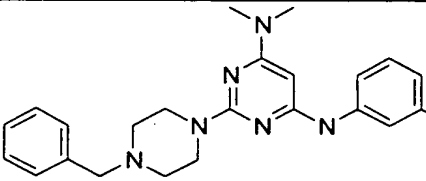
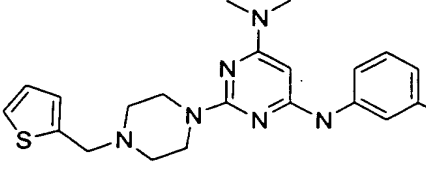
154		441
155		316
156		61
157		273
158		941
159		180

Table 3a.

160		26
161		114
162		42
163		500
164		60
165		139*

\* The binding assay normally used for the indolone compounds was used to test this compound.

Table 3a.

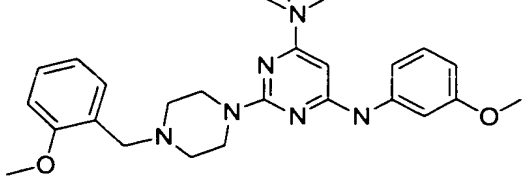
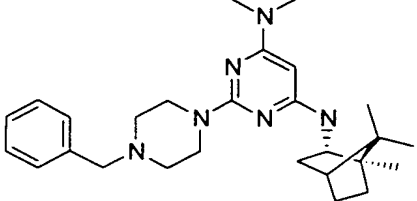
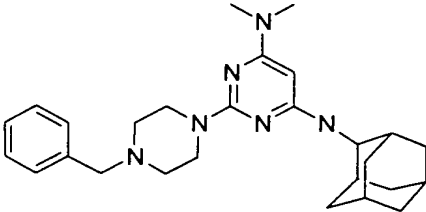
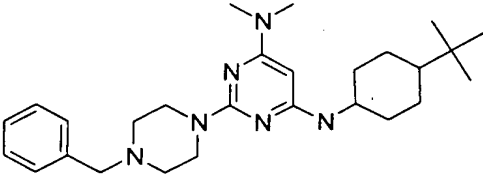
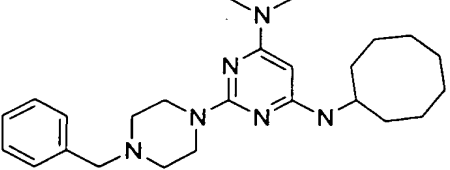
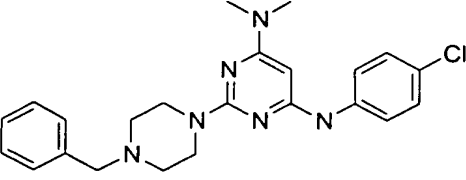
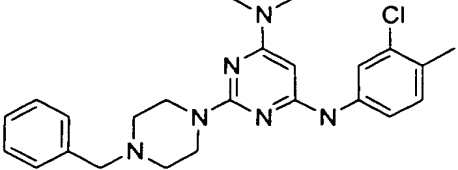
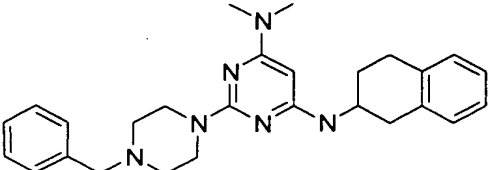
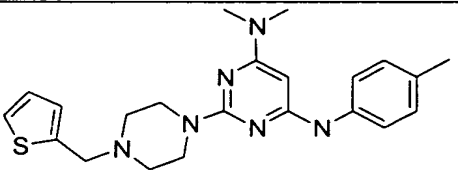
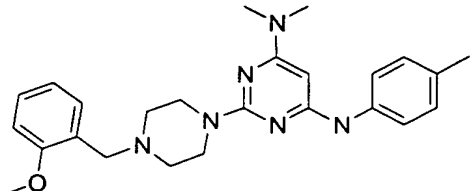
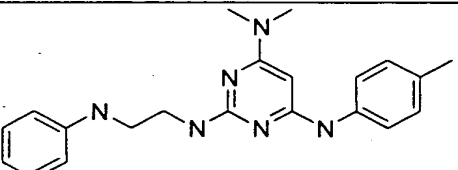
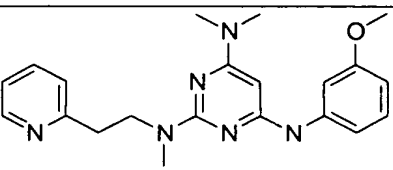
166		263
167		50
168		50
169		77
170		91
171		25

Table 3a.

172		20
173		117
174		325*
175		56
176		608
177		142

\* The binding assay normally used for the indolone compounds was used to test this compound.

Table 3a.

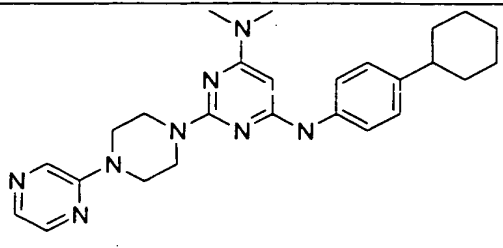
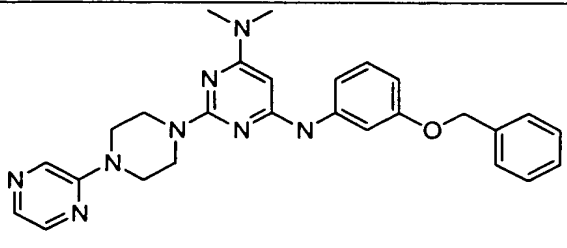
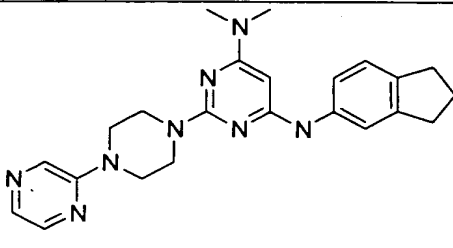
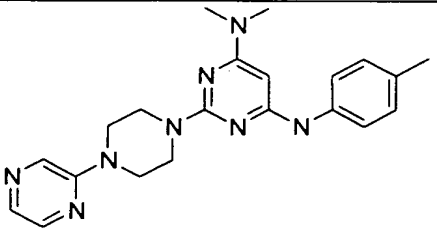
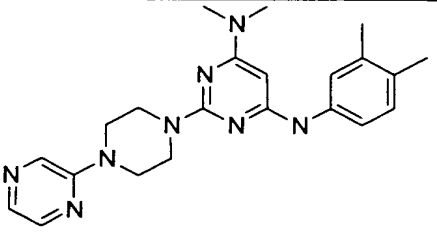
178		26
179		15
180		151
181		750
183		66

Table 3a.

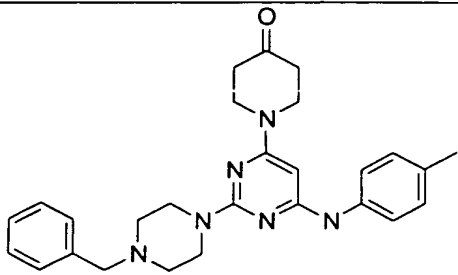
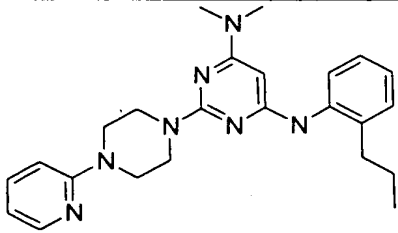
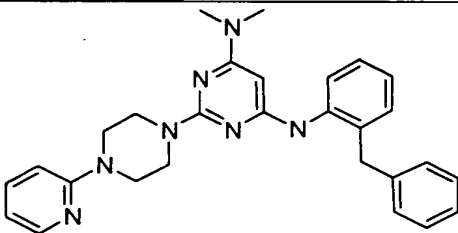
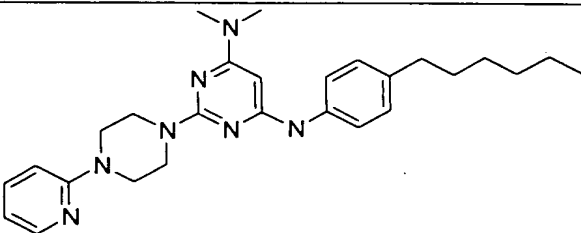
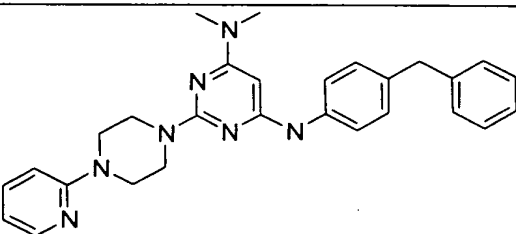
184		163
185		365
186		69
187		19
188		27

Table 3a.

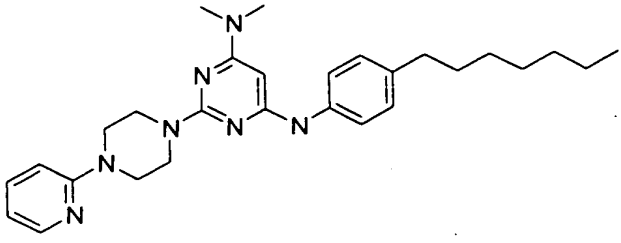
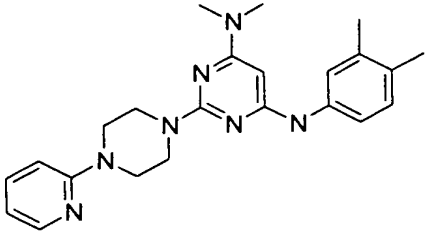
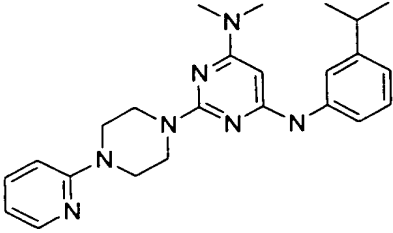
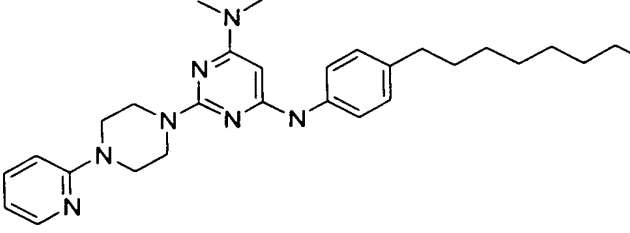
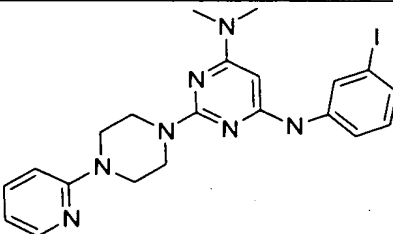
189		26
190		153
191		75
192		18
193		244

Table 3a.

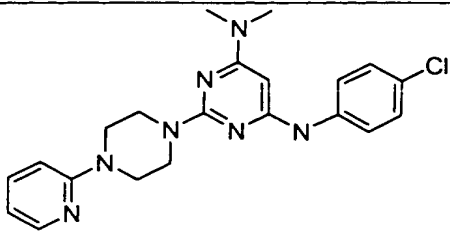
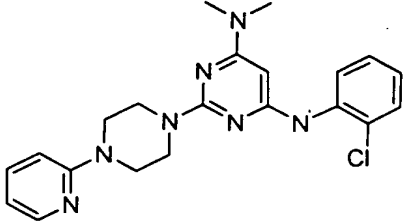
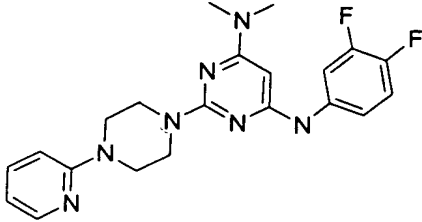
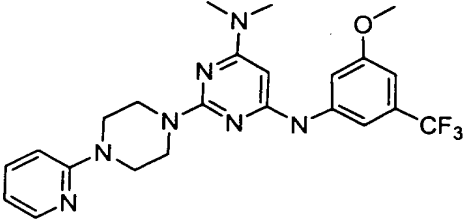
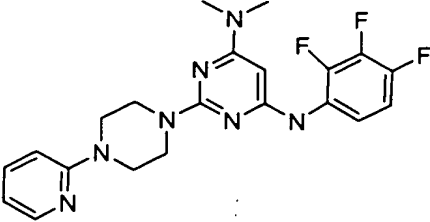
194	 <chem>CN(C)c1cc(Nc2ccc(Cl)cc2)nnc1N3CCN(Cc4ccncc4)CC3</chem>	248
195	 <chem>CN(C)c1cc(Nc2cccc(Cl)c2)nnc1N3CCN(Cc4ccncc4)CC3</chem>	388
196	 <chem>CN(C)c1cc(Nc2cc(F)c(F)cc2)nnc1N3CCN(Cc4ccncc4)CC3</chem>	443
197	 <chem>CN(C)c1cc(Nc2cc(OC)cc(C(F)(F)F)c2)nnc1N3CCN(Cc4ccncc4)CC3</chem>	666
198	 <chem>CN(C)c1cc(Nc2cc(F)c(F)c(F)c2)nnc1N3CCN(Cc4ccncc4)CC3</chem>	560



Table 3a.

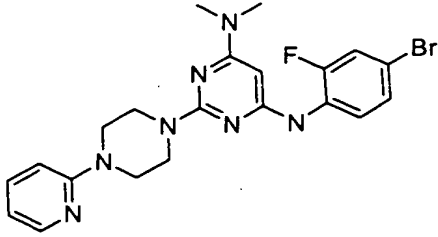
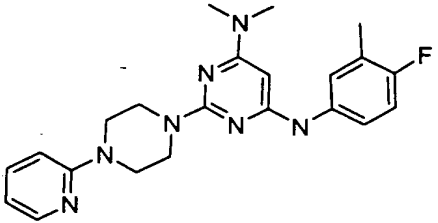
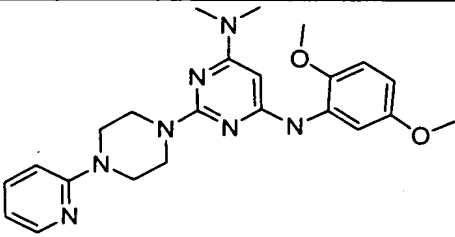
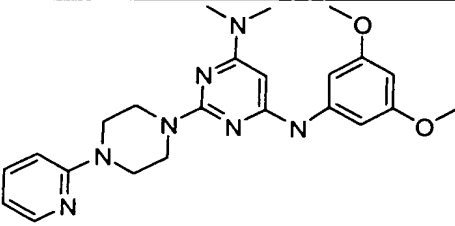
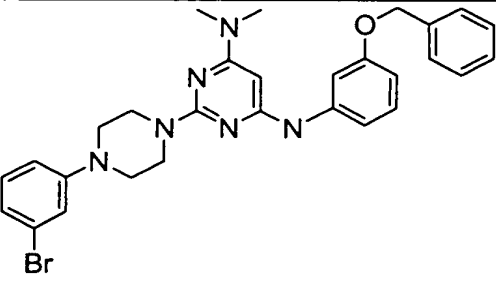
199		199
200		311
201		566
202		740
203		52

Table 3a.

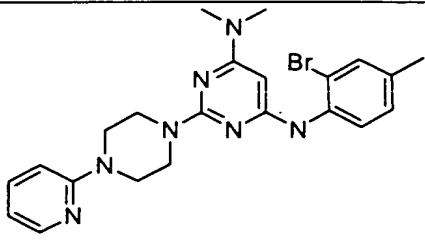
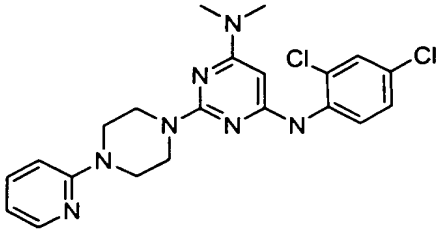
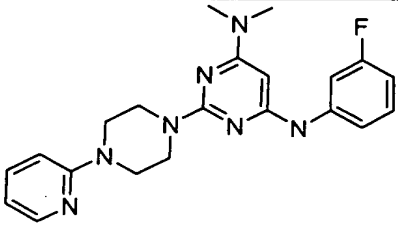
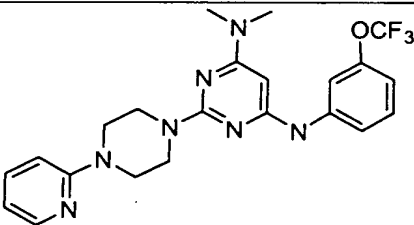
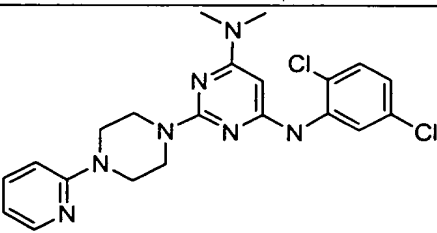
204		269
205		193
206		454
207		58
208		120

Table 3a.

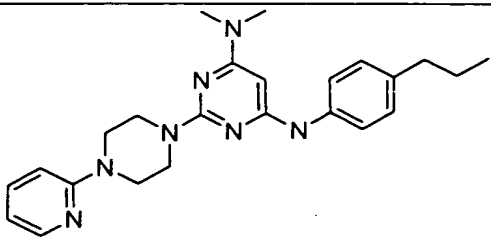
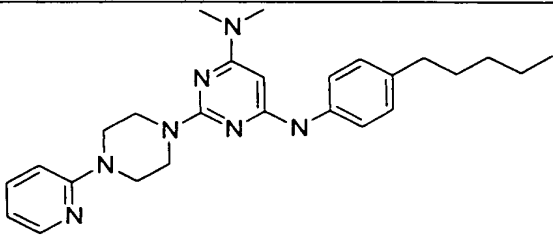
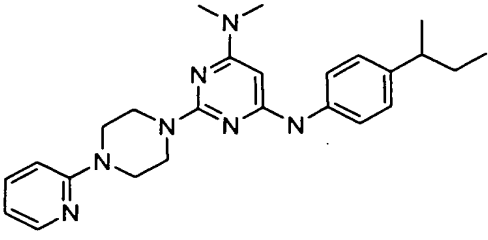
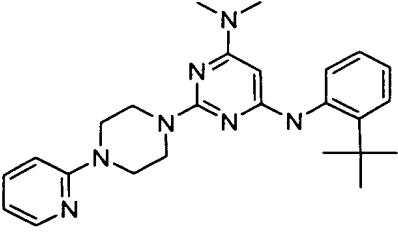
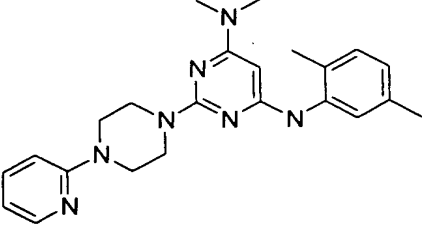
209		205
210		58
211		58
212		231
213		165

Table 3a.

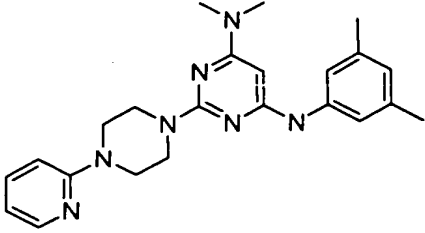
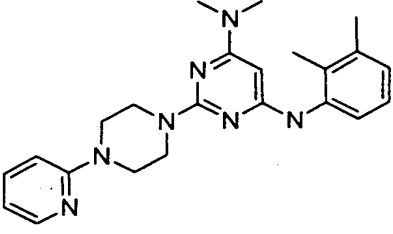
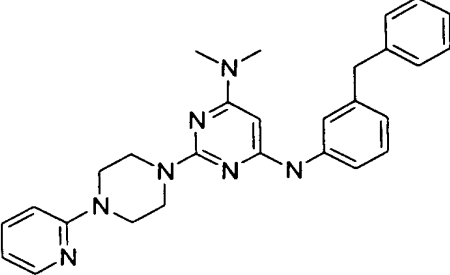
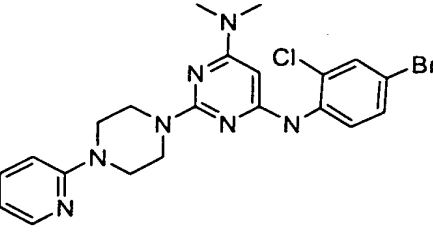
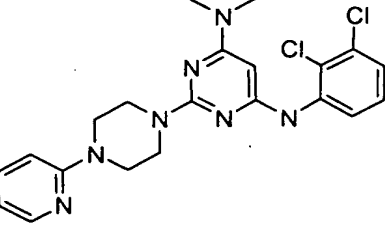
214		676
215		450
216		50
217		190
218		616

Table 3a.

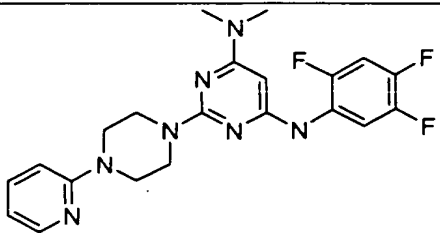
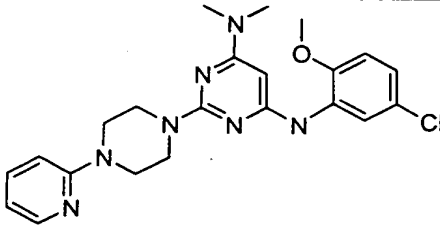
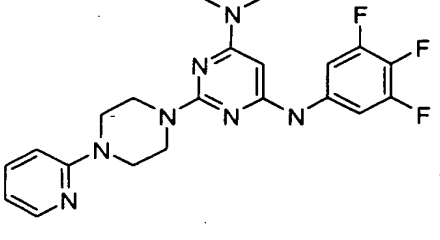
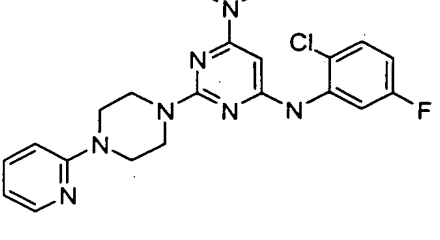
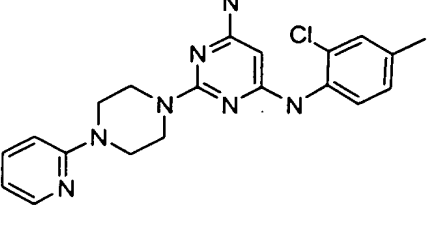
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220	 <chem>CN(C)c1nc(NC2CCN(CC2)c3ccncc3)c4ccc(OC)c(Cl)c4</chem>	708
221	 <chem>CN(C)c1nc(NC2CCN(CC2)c3ccncc3)c4cc(F)c(F)c(F)c4</chem>	213
222	 <chem>CN(C)c1nc(NC2CCN(CC2)c3ccncc3)c4cc(Cl)c(F)cc4</chem>	847
223	 <chem>CN(C)c1nc(NC2CCN(CC2)c3ccncc3)c4cc(Cl)cc(C)c4</chem>	559

Table 3a.

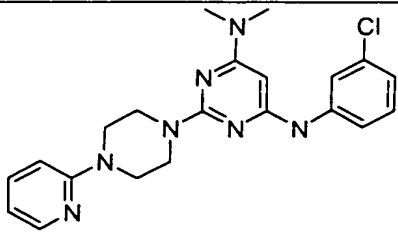
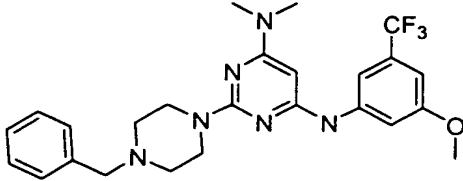
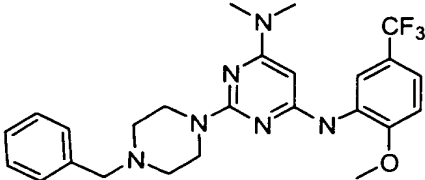
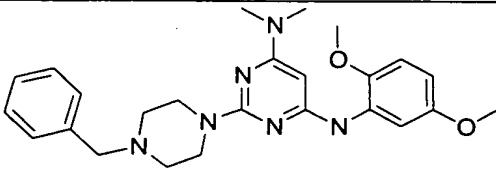
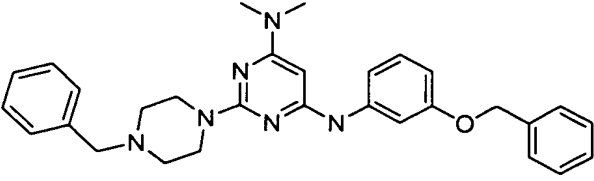
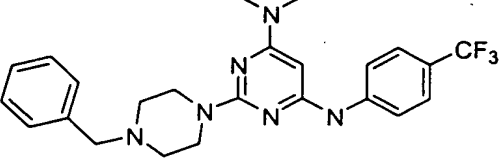
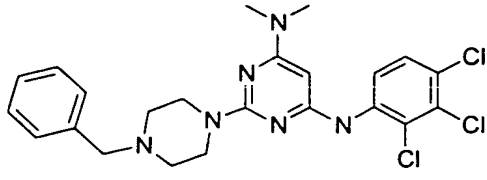
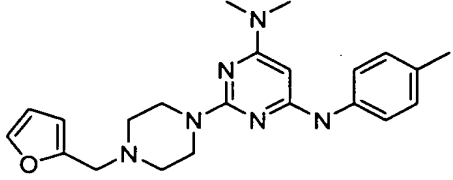
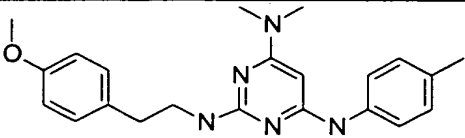
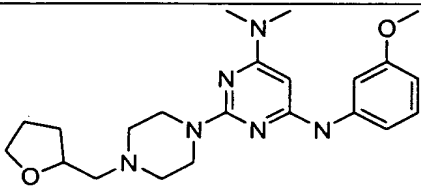
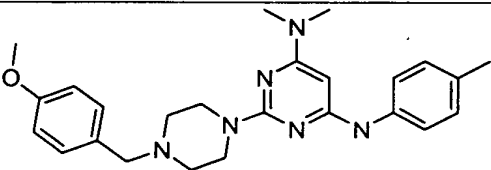
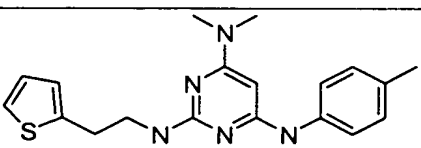
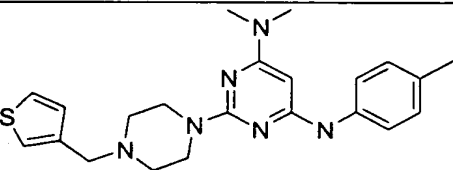
224		218
225		66
226		72
227		600
228		32
229		37

Table 3a.

230		52
231		136
232		155*
233		869
235		114*
237		404*
238		331*

\* The binding assay normally used for the indolone compounds was used to test this compound.

Table 3a.

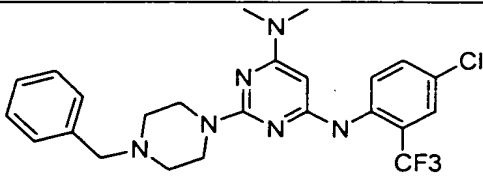
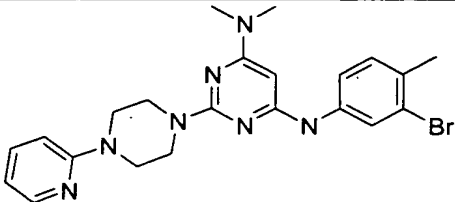
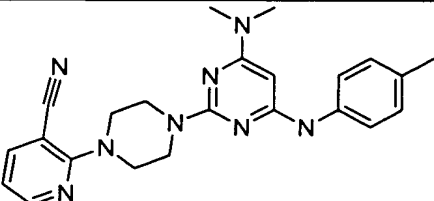
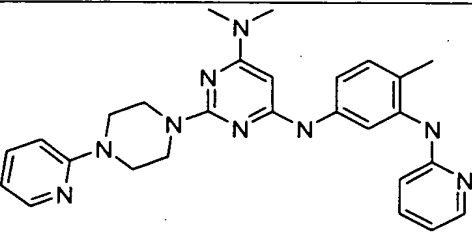
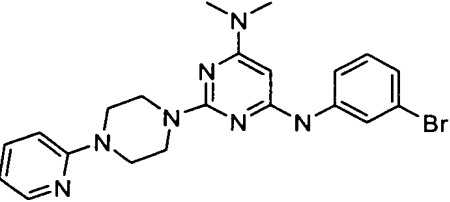
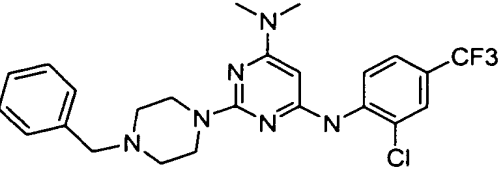
39		59
240		77
241		261
242		166
243		46
244		55



Table 3a.

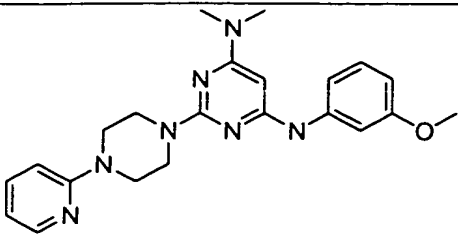
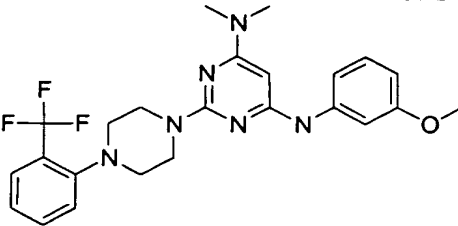
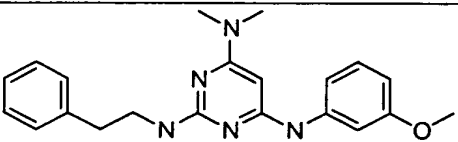
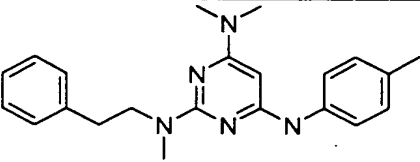
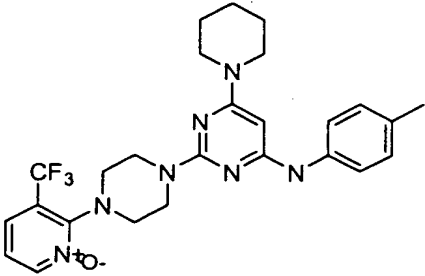
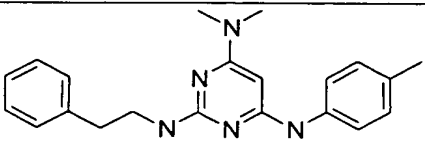
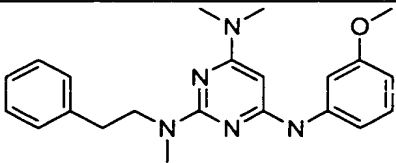
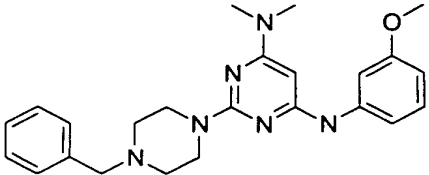
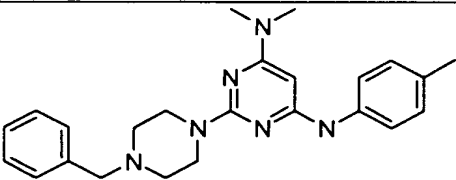
245		537
246		270
247		195
248		33
249		386
250		119

Table 3a.

251		54
252		88
253		49

## B. General Procedure for Preparing Indolones

General Procedure for Synthesis of Iminoisatins. The appropriately substituted isatin (10 mg - 10 g) was placed in a flask and the appropriate aniline (1.0 - 1.1 equivalents) was added and the mixture was stirred to homogeneity. The mixture was then heated to 110 °C for 2-7 hours and then cooled. Solids were crystallized from hot methanol and filtered, giving the desired products (usually as an inseparable interconverting mixture of E/Z isomers).

## Procedure A:

1-(3-THIENYL)-1H-INDOLE-2,3-DIONE: Triethylamine (56.9 mL, 0.408 mol), was added to a mixture of 1H-indole-2,3-dione (15.0 g, 0.102 mol), copper (II) acetate (46.0 g, 0.255 mol), and 3-thienylboronic acid (19.6 g, 0.153 mol) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL). The reaction mixture was stirred overnight, filtered through Celite, rinsed with EtOAc/hexane (1:1, 300 mL), and concentrated in vacuo. The crude product was purified by column chromatography on silica using Hexane/EtOAc (1:1), giving the desired product (1.1 g, 50 %).

## 25 Procedure B:

(3E)-3-[(4-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: A solution of 1-(3-Thienyl)-1H-indole-

2,3-dione (20 mg, 0.087 mmol) in 1% HOAc/MeOH (8 mL) was added to a solution of *p*-toluidine (19 mg, 0.18 mmol) in 1% HOAc/MeOH (8 mL). The reaction mixture was stirred for 12 h at room temperature, heated at 50 °C for 1 h, and concentrated in vacuo. The residue was purified by preparative TLC on silica using EtOAc/hexanes (3:7, 0.1 % TEA) giving the desired product (14 mg, 50%).

Procedure C:

10     (3Z)-1-PHENYL-3-{[4-(3-THIENYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE:     A     mixture     of     (3Z)-3-[(4-bromophenyl)imino]-1-phenyl-1,3-dihydro-2H-indol-2-one (50.0 mg, 0.133 mmol), thiophene-3-boronic acid (26.0 mg, 0.199 mmol), tetrakis(triphenylphosphine)palladium(0) (31.0 mg, 0.0268 mmol in THF (5 mL), and aqueous Na<sub>2</sub>CO<sub>3</sub> (2M, 100 µL) was heated at 67 °C for 24 h. The crude product was concentrated in vacuo and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL), and concentrated. The crude product was purified by preparative TLC using 10 % methanol in CHCl<sub>3</sub>, giving the desired product (18 mg, 35%).

## Procedure D:

(3Z)-5-BROMO-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-

DIHYDRO-2H-INDOL-2-ONE: A mixture of 5-bromo-1H-indole-

5 2,3-dione (1.0 g, 0.442 mmol) and 3-trifluoromethylaniline (0.993 g, 6.2 mmol) in a solution of 1% acetic acid in methanol was stirred at 50 °C for 12 h. The crude product was concentrated in vacuo, giving the desired crude product (640 mg, 40%).

10

## Procedure E:

(3Z)-5-BROMO-1-PHENYL-3-{[3-

(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-

ONE: A mixture of (3Z)-5-bromo-3-{[3-

15 (trifluoromethyl)phenyl]imino}-1,3-dihydro-2H-indol-2-one (100 mg, 0.272 mmol), copper (II) acetate (54 mg, 0.33 mmol), triethylamine (82.8 mg, 0.817 mmol), and benzene boronic acid (40 mg, 0.325 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 12 h. The crude mixture  
20 was concentrated in vacuo and purified by preparative TLC using EtOAc:hexane (3:7, 1% triethylamine), giving the desired product (22 mg, 20%).

## Procedure F:

(3Z)-1,5-DIPHENYL-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-  
1,3-DIHYDRO-2H-INDOL-2-ONE: A mixture of (3z)-5-bromo-1-  
 phenyl-3-{[3-(trifluoromethyl)phenyl]imino}-1,3-dihydro-  
 5 2H-indol-2-one (22 mg, 0.05 mmol),  
 tetrakis(triphenylphosphine)palladium(0) (12.0 mg, 0.01  
 mmol), benzene boronic acid (10 mg, 0.08 mmol) in THF (5  
 mL), and aqueous Na<sub>2</sub>CO<sub>3</sub> (2M, 100 µL) was heated at 67 °C  
 for 24 h. The crude product was concentrated in vacuo  
 10 and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 ml),  
 concentrated, and purified by preparative TLC using 10 %  
 methanol in CHCl<sub>3</sub>, giving the desired product (4 mg, 18%).

## Procedure G:

15 ETHYL 5-[(2,3-DIOXO-2,3-DIHYDRO-1H-INDOL-1-YL) METHYL]-2-  
FUROATE: A mixture of ethyl 5-(chloromethyl)-2-furoate  
 (148 mg, 1.01 mmol) in dioxane (15 ml) was added to a  
 mixture of NaH (48 mg, 1.20 mmol) in dioxane (10 mL)  
 under argon at 0 °C. The mixture was stirred for 1 h at  
 20 room temperature, refluxed under argon for 16 h, cooled  
 to room temperature, and then concentrated in vacuo. The  
 residue was purified by preparative TLC using  
 EtOAc/hexane (3:7), giving the desired product (56 mg, 19  
 %).

## Procedure H:

ETHYL 5-[(3Z)-2-oxo-3-{[3-(trifluoromethyl)phenyl]imino}-2,3-dihydro-1H-indol-1-

5 YL)methyl]-2-furoate: A mixture of ethyl 5-[(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)methyl]-2-furoate (60 mg, 0.200 mmol) and 3-trifluoromethylaniline (32 mg, 0.200 mmol) was heated at 140 °C for 2 h. The residue was dissolved in CHCl<sub>3</sub> (1 mL) and purified by preparative TLC using  
 10 EtOAc/hexane (6:4), giving the desired product (20 mg, 23 %).

## Procedure I:

6-Methoxy-1-phenyl-1H-indole-2,3-dione: A solution of N-(3-methoxyphenyl)-N-phenylamine (1.14 g, 5.72 mmol) in ether (3 mL) was added to a solution of oxalyl chloride (728 g, 5.75 mmol) and heated at reflux for 1 h. The resulting mixture was cooled to room temperature, concentrated to dryness, and redissolved in nitrobenzene (35 mL). The  
 15 solution was added to a solution of AlCl<sub>3</sub> in nitrobenzene (0.762 g, 5.72 mmol), and the resulting mixture was  
 20 heated at 70 °C for 16 h. The crude product was concentrated in vacuo and purified by column

chromatography using EtOAc/hexane (1:1), giving the desired product 60, mg, 50 %).

Procedure J:

5     (3Z)-1-(4-BROMOPHENYL)-3-{[3-  
       (TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2H-INDOL-2-  
       ONE:           A           solution           of           (3Z)-3-{[3-

      (trifluoromethyl)phenyl]imino}-1,3-dihydro-2H-indol-2-one

      (100 mg, 0.344 mmol), copper (II) acetate (93 mg, 0.516

10    mmol), triethylamine (105 mg, 1.03 mmol) , and 4-

      bromobenzene boronic acid (104 mg, 0.516 mmol) in 5 mL of

      CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 12 h. The crude

      mixture was concentrated in vacuo and purified by

      preparative TLC using EtOAc:hexane (3:7, 1%

15    triethylamine), giving the desired product (65 mg, 42%).

Procedure K:

A       solution       of       (3Z)-1-(4-bromophenyl)-3-{[3-

      (trifluoromethyl)phenyl]imino}-1,3-dihydro-2H-indol-2-one

20    (30 mg, 0.068), tetrakis(triphenylphosphine)palladium(0)

      (16.0 mg, 0.014 mmol), benzene boronic acid (13 mg,

      0.101 mmol) in THF (5 mL), and aqueous Na<sub>2</sub>CO<sub>3</sub> (0.45 M, 300

      μL) was heated at 67 °C for 40 h. The crude product was

      concentrated in vacuo and the residue was extracted with



CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 ml), concentrated, and purified by preparative TLC using 10 % methanol in CHCl<sub>3</sub>, giving the desired product (5 mg, 16%).

5 The compounds of Examples 92 - 107, inclusive, were purchased from Bionet Research Ltd., 3 Highfield Industrial Estate, Camelford, Cornwall PL32 9QZ, UK. These compounds can also be synthesized using the procedure described above.

10

Example 91: 3 - [(2-METHOXYPHENYL) IMINO] - 1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

15 Example 92: 1-PHENYL-3- [[3-(TRIFLUOROMETHYL) PHENYL] IMINO] - 1,3-DIHYDRO-2H-INDOL-2-ONE

Example 93: 3 - [(3-METHYLPHENYL) IMINO] - 1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

20 Example 94: 3 - [(3-CHLOROPHENYL) IMINO] - 1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 95: 1-PHENYL-3- [[4-(TRIFLUOROMETHYL) PHENYL] IMINO] - 1,3-DIHYDRO-2H-INDOL-2-ONE

25

Example 96: 3 - [(4-METHYLPHENYL) IMINO] - 1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

30 Example 97: 3 - [(4-CHLOROPHENYL) IMINO] - 1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 98: 3-[(4-BROMOPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

5 Example 99: 3-[(4-FLUOROPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 100: 3-[(4-PHENOXYPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

10 Example 101: 3-[(4-ETHOXYPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 102: 3-[(4-METHOXYPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

15 Example 103: 3-[(3,5-DICHLOROPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

20 Example 104: 3-[(3,5-DIMETHYLPHENYL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE

Example 105: 1-ALLYL-3-[(3,4-DICHLOROPHENYL) IMINO]-1,3-DIHYDRO-2H-INDOL-2-ONE

25 Example 106: 1-ALLYL-3-[(3,5-DICHLOROPHENYL) IMINO]-1,3-DIHYDRO-2H-INDOL-2-ONE

30 Example 107: 3-[(4-BROMOPHENYL) IMINO]-1-ISOPROPYL-1,3-DIHYDRO-2H-INDOL-2-ONE

The methods that follow demonstrate procedures useful for synthesizing compounds of this invention (illustrated in

Schemes 6 and 7). Substituted isatins useful for synthesizing compounds of this invention can alternatively be obtained using the procedures described in the following references:

- 5 Garden, S. J.; Da Silva, L. E.; Pinto, A.C.; *Synthetic Communications*, 1998, 28, 1679 - 1689.
- Coppola, G.M.; *Journal of Heterocyclic Chemistry*, 1987, 24, 1249.
- 10 Hess, B.A. Jr; Corbino, S.; *Journal of Heterocyclic Chemistry*, 1971, 8, 161.
- Bryant, W. M. III; Huhn, G.F.; Jensen, J.H.; Pierce, M. E.; Stambach, C.; *Synthetic Communications*, 1993, 23, 1617 - 1625.

15 Example 108: 1-[(5-CHLORO-2-THIENYL)METHYL]-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: A mixture of 1-[(5-chloro-2-thienyl)methyl]-2H-indole-2,3-dione (25 mg, 0.09 mmol) (prepared as described below) and 3-trifluoromethylaniline (11.3  $\mu$ L, 0.09 mmol) was heated neat at 140 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 3:7 ethyl acetate in hexane as the eluent, giving the desired product (23 mg 0.05 mmol, 61 %). <sup>1</sup>H NMR (400 MHz):  $\delta$  (major isomer) 7.57 (t, *J* = 7.7, 1H), 7.53 (t, *J* = 7.8, 1H), 7.33 (t, *J* = 7.8, 1H), 7.28 (s, 1H), 7.19 (d, *J* = 7.6, 2H), 6.94 - 6.72 (m, 4H), 6.56 (d, *J* = 7.7, 1H), 5.02 (s, 2H); ESI-MS *m/z* found 421 (MH<sup>+</sup>).

20

25

1-[(5-CHLORO-2-THIENYL)METHYL]-2H-INDOLE-2,3-DIONE: A solution of isatin (125 mg, 0.85 mmol) in anhydrous dioxane (10 mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil, 24 mg,

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0.62 mmol) in anhydrous dioxane (10 mL) at 0 °C under argon. The mixture was allowed to stir for 5 minutes and then 2-chloro-5-(chloromethyl)thiophene (0.12 mL, 1.02 mmol) in dioxane (10 mL) was added dropwise to the resulting mixture. The reaction mixture was heated at reflux under argon for 16 h and concentrated *in vacuo*. The crude material was purified preparative TLC using 1:24 methanol in chloroform as the eluent, giving the desired product as a yellow solid (53 mg, 0.19 mmol, 22 %). <sup>1</sup>H NMR (400 MHz): δ 7.62 (d, *J* = 7.4, 1H), 7.56 (t, *J* = 7.8, 1H), 7.14 (t, *J* = 7.7, 1H), 6.94 (d, *J* = 8.0, 1H), 6.90 (d, *J* = 3.2, 1H), 6.78 (d, *J* = 3.7, 1H), 4.90 (s, 2H).

Example 109: 1-(3-THIENYL)-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: A mixture of 1-(3-thienyl)-2H-indole-2,3-dione (25 mg, 0.11 mmol) (prepared as described below) and 3-trifluoromethylaniline (14 uL, 0.11 mmol) was heated neat at 140 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 3:7 ethyl acetate and hexane as the eluent, giving the desired product as a yellow solid (7.3 mg, 0.02 mmol, 22 %). <sup>1</sup>H NMR (400 MHz) δ 7.62 - 7.19 (m, 9H), 6.94 (d, *J* = 8.0, 1H), 6.76 (t, *J* = 7.6, 1H); ESI-MS *m/z* found 373 (MH<sup>+</sup>).

1-(3-THIENYL)-2H-INDOLE-2,3-DIONE: Copper(II) acetate monohydrate (4.25 g, 23.4 mmol) was heated at reflux in acetic anhydride (30 mL) for 2 h. The mixture was filtered and washed with anhydrous ether (500 mL). The solid was dried *in vacuo* at 55 °C for 16 h. Dichloromethane (1 mL) was added to a mixture of

copper(II) acetate (62 mg, 0.34 mmol), isatin (50 mg, 0.34 mmol), and thiophene-3-boronic acid (87 mg, 0.68 mmol), followed by triethylamine (0.10 mL, 0.68 mmol) under argon. The resulting solution was stirred for 16 h at room temperature. The reaction mixture was then recharged with 0.10 mmol copper(II) acetate, 0.10 mmol of 3-thiophene boronic acid, and 1 drop of triethylamine, and the mixture was heated at 50 °C for 6 h. The crude material was purified by preparative TLC using 3:97 methanol in chloroform as the eluent, giving the desired product as a yellow solid (25 mg, 0.11 mmol, 33 %). <sup>1</sup>H NMR (400 MHz): δ 7.70 (d, *J* = 7.5, 1H), 7.58 (t, *J* = 7.8, 1H), 7.50 (d, *J* = 5.1, 1H), 7.48 (s, 1H), 7.24 (d, *J* = 5.1, 1H), 7.18 (t, *J* = 7.51, 1H), 7.05 (d, *J* = 8.0, 1H).

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Example 110: 2-METHYL-5-[(2-OXO-1-PHENYL-1,2-DIHYDRO-3H-INDOL-3-YLIDENE)AMINO]-2H-ISOINDOLE-1,3(2H)-DIONE: A mixture of 1-phenylisatin (50 mg, 0.22 mmol) and 4-amino-N-methylphthalimide (40 mg, 0.22 mmol) was heated neat at 215 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 3:7 ethyl acetate and hexane as the eluent, giving the desired product as a yellow solid (8 mg, 0.02 mmol, 10 %). <sup>1</sup>H NMR (400 MHz): δ 7.88 (d, *J* = 7.8, 1H), 7.83 - 7.80 (m, 1H), 7.51 (t, *J* = 7.5, 1H), 7.47 - 7.18 (m, 6H), 7.02 (t, *J* = 8.0, 1H), 6.91 - 6.79 (m, 2H), 6.58 (d, *J* = 7.5, 1H), 3.22 (s, 3H); ESI-MS *m/z* found 382 (MH<sup>+</sup>).

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Example 111: 1-[(5-CHLORO-1-BENZOTHIEN-3-YL)METHYL]-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2H-INDOL-

2-ONE: A mixture of 1-[(5-chloro-1-benzothien-3-yl)methyl]-2H-indole-2,3-dione (50 mg, 0.15 mmol) (prepared as described below) and 3-trifluoromethylaniline (0.020 mL, 0.15 mmol) was heated  
 5 neat at 140 °C for 2 h. The crude material was purified by preparative TLC using a mixture of 1:3 ethyl acetate and hexane as the eluent giving the desired product as a yellow solid (13 mg, 0.030 mmol, 18%). <sup>1</sup>H NMR (400 MHz):  
 10 δ 7.98 (d, *J* = 2.0, 1H), 7.80 (d, *J* = 8.6, 1H), 7.58 (t, *J* = 7.7, 1H), 7.52 (d, *J* = 8.1, 1H), 7.43 (s, 1H), 7.38 (dd, *J* = 8.6, 1.9, 1H), 7.31 (overlapping singlet and dt, *J* = 1.2, 7.8, 2H), 7.24 (d, *J* = 7.8, 1H), 6.87 (d, *J* = 7.9, 1H), 6.77 (t, *J* = 7.7, 1H), 6.59 (d, *J* = 7.7, 1H),  
 15 5.20 (s, 2H). ESI-MS *m/z* found 471 (MH<sup>+</sup> with <sup>35</sup>Cl), 473 (MH<sup>+</sup> with <sup>37</sup>Cl).

1-[(5-CHLORO-1-BENZOTHIEN-3-YL)METHYL]-2H-INDOLE-2,3-dione: A solution of isatin (125mg, 0.85 mmol) in anhydrous dioxane (10 mL) was added dropwise to a  
 20 solution of sodium hydride (60% dispersion in mineral oil, 25 mg, 0.62 mmol) in anhydrous dioxane (10 mL) at 0 °C under argon. The mixture was allowed to stir for 5 minutes and then a solution of 3-(bromomethyl)-5-chlorobenzo[b]thiophene (267 mg, 1.02 mmol) in dioxane  
 25 (10 mL) was added dropwise to the reaction mixture. The reaction mixture was heated at reflux under argon for 16 h and concentrated in vacuo. The crude material was purified by preparative TLC using 1:24 methanol in chloroform as the eluent, giving the desired product as a  
 30 yellow solid (125 mg, 0.38 mmol, 45%). <sup>1</sup>H NMR (400 MHz): δ 7.89 (s, 1H), 7.79 (d, *J* = 8.5, 1H), 7.65 (d, *J* = 7.5, 1H), 7.54 (t, *J* = 8.0, 1H), 7.42 (s, 1H), 7.38 (d, *J* =

8.5, 1H), 7.14 (t,  $J = 7.5$ , 1H), 6.88 (d,  $J = 7.8$ , 1H), 5.13 (s, 2H).

Example 112: 3-(1H-INDOL-5-YLIMINO)-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: 1-phenylisatin (51.8 mg, 0.23 mmol) and 5-aminoindole (31 mg, 0.23 mmol) were mixed and heated at 140 °C for 2 h. The resulting crude product was purified by preparative TLC using ethyl acetate/hexane (6:4) as the eluent, giving the desired product as a yellow solid (10.8 mg, 14%).  $^1\text{H}$  NMR (400 MHz):  $\delta$  8.28 (s, 1H), 7.57 (t,  $J = 7.7$ , 2H), 7.49 - 7.40 (m, 6H), 7.29 - 7.23 (m, 1H), 7.03 (dd,  $J = 8.5$ , 1.7, 1H), 6.98 (d,  $J = 7.6$ , 1H), 6.83 (d,  $J = 8.0$ , 1H), 6.74,  $J = 7.6$ , 1H), 6.59 (s, 1H); ESI-MS  $m/z$  found 338 ( $\text{MH}^+$ ).

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Example 113: 3-[(6-CHLORO-3-PYRIDINYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: 1-phenylisatin (23.0 mg, 0.10 mmol) and 5-amino-2-chloropyridine (12.8 mg, 0.10 mmol) were mixed and heated at 140 °C for 7 h. The resulting crude product was purified by preparative TLC using hexane/ethyl acetate (8:2) as the eluent, giving the desired product as a yellow solid (19.7 mg, 59%).  $^1\text{H}$  NMR (400 MHz)  $\delta$  8.15 (d,  $J = 8$ , 1H), 7.6 - 7.2 (m, 9H), 6.85 - 6.75 (m, 2H); ESI-MS  $m/z$  found 334 ( $\text{MH}^+$ ).

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Example 114: 3-[(2-METHYL-1,3-BENZOTHAZOL-5-YL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: 5-amino-2-methylbenzothiazole (52.2 mg, 0.31 mmol) was mixed with 1-phenylisatin (69.7 mg, 0.31 mmol) and heated at 140 °C for 3 h. The resulting crude product was purified by preparative TLC using ethyl acetate/hexane (6:4) as the

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eluent to give the desired product as a yellow solid (36.9 mg, 32.3 %).  $^1\text{H}$  NMR Data:  $\delta$  7.9-6.7 (m, 12H), 2.9 (s, 3H). ESI-MS  $m/z$  found 370 ( $\text{MH}^+$ ).

5     Example 254: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-(2-PYRIDINYLMETHYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures H and K (for substitution of 2-picoly chloride).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 - 8.46 (m, 1H), 7.87 - 7.78 (m, 1H), 7.64 (d, 1H,  $J = 7.1$ ), 7.53 - 7.31  
10 (m, 5H), 7.28 (d, 1H,  $J = 4.1$ ), 7.12 (d, 1H,  $J = 8.1$ ), 6.58-6.53 (m, 1H), 5.51 (s, 2H); ESI-MS  $m/z$  381 ( $\text{MH}^+$ ).

Example 255: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-[(3,5-DIMETHYL-4-ISOXAZOLYL)METHYL]-1,3-DIHYDRO-2H-INDOL-2-ONE:  
15 Prepared by Procedure B (microwave heating).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (d, 1H,  $J = 9.1$ ), 7.46 (dt, 1H,  $J = 8.1, 2.0$ ), 7.28 (d, 1H,  $J = 2.1$ ), 7.02 (d, 1H,  $J = 2.0$ ), 6.88 (dt, 1H,  $J = 8.0, 2.1$ ), 6.74 - 6.72 (m, 1H), 6.72 - 6.70 (m, 1H), 5.53 (s, 2H), 2.50 (s, 3H), 2.24 (s, 3H);  
20 ESI-MS  $m/z$  399 ( $\text{MH}^+$ ).

Example 256: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-[3-(TRIFLUOROMETHYL)PHENYL]-1,3-DIHYDRO-2H-INDOL-2-ONE:  
Prepared by Procedures A and B.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$   
25 7.90 - 7.87 (m, 1H), 7.83 - 7.79 (m, 1H), 7.67 (d, 1H,  $J$



= 8), 7.46 - 7.40 (m, 1H), 7.33 (d, 1H,  $J = 2$ ), 7.08 - 7.05 (m, 1H), 6.96 - 6.80 (m, 5H); ESI-MS  $m/z$  435 ( $MH^+$ ).

Example 257: (3Z)-1-(3,5-DICHLOROPHENYL)-3-[(3,4-DICHLOROPHENYL)IMINO]-1,3-DIHYDRO-2H-INDOL-2-ONE:

Prepared by Procedures A and B.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.93 (d, 1H,  $J = 8.1$ ), 7.79 (d, 1H,  $J = 6.0$ ), 7.72 - 7.68 (m, 1H), 7.59 - 7.45 (m, 1H), 7.46 (d, 1H,  $J = 8.1$ ), 7.32 (dt, 1H,  $J = 8.0, 2.1$ ), 7.23 (d, 1H,  $J = 2.5$ ), 6.97 (dd, 1H,  $J = 8.0, 2.1$ ), 6.92 - 6.87 (m, 1H), 6.85 - 6.81 (m, 1H); ESI-MS  $m/z$  435 ( $MH^+$ ).

Example 258: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-6-METHOXY-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by

Procedures K, L, and B.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.69 - 7.54 (m, 1H), 7.53 - 7.38 (m, 3H), 7.29 (d, 1H,  $J = 2.0$ ), 7.17 (d, 1H,  $J = 8.1$ ), 7.12 (d, 1H,  $J = 8.0$ ), 6.84 (d, 1H,  $J = 2.5$ ), 6.78 (d, 1H,  $J = 8$ ), 6.6 (dd, 2H,  $J = 8.0, 2.0$ ), 6.55 (dd, 2H,  $J = 8.1, 2.5$ ); ESI-MS  $m/z$  (398  $MH^+$ ).

Example 259: (3Z)-3-[(4-CHLORO-3-METHYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by

Procedures A and B (80 °C).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.69 - 7.62 (m, 2H), 7.49 (s, 1H), 7.47 (s, 1H), 7.41 (dt, 1H,

$J = 7.1, 1.6$ ), 7.3 (dd, 1H,  $J = 5.0, 1.6$ ), 7.05 - 6.97 (m, 1H, 6.93 - 6.86 (m, 1H), 6.77 (m, 1H), 6.56 (m, 1H), 2.53 (s, 3H); ESI-MS  $m/z$  353 ( $MH^+$ ).

5 Example 260: (3Z)-3-(2-NAPHTHYLIMINO)-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and B (80 °C).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.15 (d, 1H,  $J = 9.1$ ), 8.06 - 7.99 (m, 1H), 7.89 - 7.80 (m, 1H), 7.78 - 7.71 (m, 1H), 7.71 - 7.47 (m, 4H), 7.41 - 7.35 (m, 1H), 7.33 (d, 10 1H,  $J = 5.2$ ), 7.28 (d, 1H,  $J = 6.8.1$ ), 7.00 (d, 1H,  $J = 8.0$ ), 6.76 (t, 1H,  $J = 7.8$ ), 6.67 (d, 1H,  $J = 7.9$ ); ESI-MS  $m/z$  355 ( $MH^+$ ).

Example 261: (3Z)-3-[(4-CHLOROPHENYL) IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and B (80 °C).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.69 - 7.56 (m, 2H), 7.54 - 7.48 (m, 1H), 7.41 (dt, 1H,  $J = 8, 2$ ), 7.32 - 7.28 (m, 1H), 7.11 - 6.99 (m, 3H), 6.89 (dt, 1H,  $J = 8$ ), 6.77 - 6.73 (m, 1H), 6.66 - 6.33 (m, 1H); 20 ESI-MS  $m/z$  339 ( $MH^+$ ).

Example 262: (3Z)-3-[(4-IODOPHENYL) IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and B (1% HOAc in MeOH).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.79 - 7.74

(m, 2H), 7.53 - 7.48 (m, 2H), 7.35 (dt, 1H,  $J = 8.0$ , 1.2), 7.29 - 7.24 (m, 1H), 6.98 (d, 1H,  $J = 8.0$ ), 6.89 - 6.75 (m, 4H); ESI-MS  $m/z$  431 ( $MH^+$ ).

5     Example     263:     (3Z)-3-[(4-METHYLPHENYL)IMINO]-1-(3-  
          THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE:     Prepared     by  
          Procedures A and B (1% HOAc in MeOH).  $^1H$  NMR (400 MHz,  
          CDCl<sub>3</sub>)  $\delta$  7.52 - 7.44 (m, 2H), 7.35 - 7.22 (m, 4H), 6.99 -  
          6.93 (m, 3H), 6.87 - 6.78 (m, 2H), 2.42 (s, 3H); ESI-MS  
 10      $m/z$  319 ( $MH^+$ ).

Example     264:     (3Z)-3-[(3,5-DIFLUOROPHENYL)IMINO]-1-(3-  
          THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE:     Prepared     by  
          Procedures A and B (1% HOAc in MeOH).  $^1H$  NMR (400 MHz,  
 15     CDCl<sub>3</sub>)  $\delta$  7.54 - 7.16 (m, 4H), 6.99 (dt, 1H,  $J = 8.2$ , 0.8),  
          6.89 (dt, 1H,  $J = 7.7$ , 1.1), 6.76 (d, 1H,  $J = 7.5$ ), 6.71  
          (tt, 1H,  $J = 9.3$ , 2.3), 6.64 - 6.57 (m, 2H); ESI-MS  $m/z$   
          341 ( $MH^+$ ).

20     Example     265:     (3Z)-3-([1,1'-BIPHENYL]-4-YLIMINO)-1-(3-  
          THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE:     Prepared     by  
          Procedures A and B (1% HOAc in MeOH).  $^1H$  NMR (400 MHz,

CDCl<sub>3</sub>) δ 7.73 – 7.12 (m, 13H), 6.99 (d, 1H, *J* = 8.0), 6.89 (d, 1H, *J* = 8.0), 6.82 (dt, 1H, *J* = 7.6, 1.0); ESI-MS *m/z* 381 (MH<sup>+</sup>).

5      Example 266:      ETHYL 3-{[(3Z)-2-oxo-1-(3-thienyl)-1,2-  
DIHYDRO-3H-INDOL-3-ylidene]amino}benzoate:      Prepared by  
Procedures A and B (1% HOAc in MeOH). <sup>1</sup>H NMR (400 MHz,  
CDCl<sub>3</sub>) δ 7.96 (d, 1H, *J* = 7.4), 7.75 - 7.17 (m, 6H), 6.98  
(d, 1H, *J* = 8.0), 6.87 - 6.78 (m, 2H), 6.63 (d, 1H, *J* =  
10      7.8), 4.45 - 4.32 (m, 2H), 1.43 - 1.33 (m, 3H); ESI-MS  
*m/z* 377 (MH<sup>+</sup>).

Example 267: (3Z)-3-[(6-CHLORO-3-PYRIDINYL) IMINO]-1-(3-  
THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by  
Procedures A and B (1% HOAc in MeOH). <sup>1</sup>H NMR (400 MHz,  
CDCl<sub>3</sub>) δ 8.21 - 6.81 (m, 10H); ESI-MS *m/z* 340.13 (MH<sup>+</sup>).

Example 268: 3Z)-3-[(4-PHENOXYPHENYL) IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by  
Procedures A and B (1% HOAc in MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85 - 6.70 (m, 16H); ESI-MS *m/z* 397 (MH<sup>+</sup>).

Example 269: (3Z)-3-[(4-BROMOPHENYL)IMINO]-1-(3-THIENYL)-  
1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and  
H.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 - 6.55 (m, 11H); ESI-MS  
5  $m/z$  383 ( $\text{MH}^+$ ).

Example 270: (3Z)-3-[(3-CHLOROPHENYL)IMINO]-1-(3-  
THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by  
Procedures A and H.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 - 6.50  
10 (m, 11H); ESI-MS  $m/z$  339 ( $\text{MH}^+$ ).

Example 271: (3Z)-3-[(3-METHYLPHENYL)IMINO]-1-(3-  
THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: : Prepared by  
Procedures A and B (1% HOAc in MeOH).  $^1\text{H}$  NMR (400 MHz,  
15  $\text{CDCl}_3$ )  $\delta$  7.67 - 6.78 (m, 11H), 2.39 (s, 3H); ESI-MS  $m/z$   
319 ( $\text{MH}^+$ ).

Example 272: (3Z)-3-[(3,4-DICHLOROPHENYL)IMINO]-1-(3-  
THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: : Prepared by  
20 Procedures A and B (1% HOAc in MeOH).  $^1\text{H}$  NMR (400 MHz,  
 $\text{CDCl}_3$ )  $\delta$  7.82 - 6.80 (m, 10H); ESI-MS  $m/z$  373 ( $\text{MH}^+$ ).

Example 273: (3Z)-1-(2-PYRIDINYLMETHYL)-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  382 ( $MH^+$ ).

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Example 274: (3Z)-3-[(3,5-DICHLOROPHENYL) IMINO]-1-(2-PYRIDINYLMETHYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  382 ( $MH^+$ ).

10 Example 275: (3Z)-1-[(3,5-DIMETHYL-4-ISOXAZOLYL) METHYL]-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  400 ( $MH^+$ ).

15 Example 276: (3Z)-3-[(3,4-DIFLUOROPHENYL) IMINO]-1-(3-PYRIDINYLMETHYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  350 ( $MH^+$ ).

Example 277: (3Z)-1-(3-PYRIDINYLMETHYL)-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  382 ( $MH^+$ ).

5 Example 278: (3Z)-3-[(3,4-DIFLUOROPHENYL) IMINO]-1-(2-PYRIDINYLMETHYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  350 ( $MH^+$ ).

10 Example 279: (3Z)-3-[(3,5-DICHLOROPHENYL) IMINO]-1-(3-PYRIDINYLMETHYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  384 ( $MH^+$ ).

15 Example 280: (3Z)-3-[(3,5-DICHLOROPHENYL) IMINO]-1-[(3,5-DIMETHYL-4-ISOXAZOLYL) METHYL]-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  402 ( $MH^+$ ).

20 Example 281: (3Z)-3-[(9-ETHYL-9H-CARBAZOL-3-YL) IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: : Prepared by Procedure H.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.28 - 6.66 (m, 16H), 4.47 - 4.35 (m, 2H), 1.55 - 1.44 (m, 3H); ESI-MS  $m/z$  416 ( $MH^+$ ).

Example 282: (3Z)-1-PHENYL-3-(5-QUINOLINYLMINO)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure H. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.38 - 9.32 (m, 1H), 8.55 - 8.50 (m, 1H), 8.01 - 6.62 (m, 12H), 6.43 - 6.35 (m, 1H); ESI-MS m/z 350 (MH<sup>+</sup>).

Example 283: (3Z)-3-[(4-IODOPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH<sub>2</sub>, 3 Å molecular sieves). ESI-MS m/z 425 (MH<sup>+</sup>).

Example 285: (3Z)-3-[(3,4-DIFLUOROPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH<sub>2</sub>, 3 Å molecular sieves). ESI-MS m/z 335 (MH<sup>+</sup>).

Example 286: (3Z)-3-[(2-CHLORO-4-METHYLPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH<sub>2</sub>, 3 Å molecular sieves). ESI-MS m/z 347 (MH<sup>+</sup> with <sup>35</sup>Cl), 349 (MH<sup>+</sup> with <sup>37</sup>Cl).

Example 287: (3Z)-3-[(2,4-DIMETHOXYPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure



B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH<sub>2</sub>, 3 Å molecular sieves). ESI-MS *m/z* 359 (MH<sup>+</sup>).

5 Example 288: 3-{[(3Z)-2-oxo-1-phenyl-1,2-dihydro-3H-indol-3-ylidene]amino}benzonitrile: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH<sub>2</sub>, 3 Å molecular sieves). ESI-MS *m/z* 324 (MH<sup>+</sup>).

10 Example 289: (3Z)-3-{[2-methyl-5-(trifluoromethyl)phenyl]imino}-1-phenyl-1,3-dihydro-2H-indol-2-one: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq RNH<sub>2</sub>, 3 Å molecular sieves). ESI-MS *m/z* 381 (MH<sup>+</sup>).

15 Example 290: (3Z)-3-[(4-chloro-3-methylphenyl)imino]-1-(3-thienyl)-1,3-dihydro-2H-indol-2-one: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 353 (MH<sup>+</sup>).

20 Example 291: (3Z)-3-(6-quinolinylimino)-1-(3-thienyl)-1,3-dihydro-2H-indol-2-one: Prepared by Procedures A and B (80 °C). ESI-MS *m/z* 356 (MH<sup>+</sup>).

Example 292: (3Z)-3-[(4-CHLOROPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS  $m/z$  339 ( $MH^+$ ).

5 Example 295: (3Z)-3-[(3-ISOPROPYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS  $m/z$  347 ( $MH^+$ ).

10 Example 296: (3Z)-3-[(4-CYCLOHEXYLPHENYL)IMINO]-1-(3-THIENYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures A and B (80 °C). ESI-MS  $m/z$  387 ( $MH^+$ ).

15 Example 297: (4-{[(3Z)-2-OXO-1-PHENYL-1,2-DIHYDRO-3H-INDOL-3-YLIDENE]AMINO}PHENYL)ACETONITRILE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq  $RNH_2$ , 3 Å molecular sieves). ESI-MS  $m/z$  339 ( $MH^+$ ).

20 Example 298: (3Z)-3-[(2,2-DIFLUORO-1,3-BENZODIOXOL-5-YL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B (0.1 % HOAc, 80 °C, 92 h, 4 eq  $RNH_2$ , 3 Å molecular sieves). ESI-MS  $m/z$  379 ( $MH^+$ ).

Example 299:    (3Z)-3-(1,3-BENZOTHAZOL-6-YLIMINO)-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure H. ESI-MS  $m/z$  356 ( $MH^+$ ).

5    Example 300:    (3Z)-1-TETRAHYDRO-2H-PYRAN-4-YL-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures G and H. ESI-MS  $m/z$  375 ( $MH^+$ ).

10    Example 301:    (3Z)-3-(1H-INDAZOL-6-YLIMINO)-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure H. ESI-MS  $m/z$  339 ( $MH^+$ ).

15    Example 302:    (3Z)-3-[(3-CHLOROPHENYL) IMINO]-6-METHOXY-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures I and H. ESI-MS  $m/z$  363 ( $MH^+$ ).

20    Example 303:    (3Z)-6-METHOXY-1-PHENYL-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures I and H. ESI-MS  $m/z$  397 ( $MH^+$ ).

Example 304:    (3Z)-1-PHENYL-3-{[4-(3-THIENYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE:  
Prepared by Procedures H and C. ESI-MS  $m/z$  381 ( $MH^+$ ).

Example 305: (3Z)-1-PHENYL-3-{[3'-(TRIFLUOROMETHYL)[1,1'-BIPHENYL]-4-YL]IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE:

Prepared by Procedures H and C. ESI-MS  $m/z$  443 ( $MH^+$ ).

5

Example 306: (3Z)-1-PHENYL-3-{[4-(3-PYRIDINYL)PHENYL]IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE:

Prepared by Procedures H and C. ESI-MS  $m/z$  376 ( $MH^+$ ).

10

Example 307: (3Z)-3-[(3-BROMOPHENYL)IMINO]-1-PHENYL-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedure B. ESI-MS  $m/z$  378 ( $MH^+$ ).

15

Example 308: (3Z)-1,5-DIPHENYL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures D, E, and F. ESI-MS  $m/z$  443 ( $MH^+$ ).

20

Example 309: (3Z)-1-[1,1'-BIPHENYL]-4-YL-3-{[3-(TRIFLUOROMETHYL)PHENYL]IMINO}-1,3-DIHYDRO-2H-INDOL-2-

ONE: Prepared by Procedures H (6 eq of aniline), J, and K. ESI-MS  $m/z$  443 ( $MH^+$ ).

5 Example 310: (3Z)-1-(4-HYDROXYPHENYL)-3-{[3-(TRIFLUOROMETHYL) PHENYL] IMINO}-1,3-DIHYDRO-2H-INDOL-2-

ONE: Prepared by Procedures H (6 eq of aniline) and E. ESI-MS  $m/z$  383 ( $MH^+$ ).

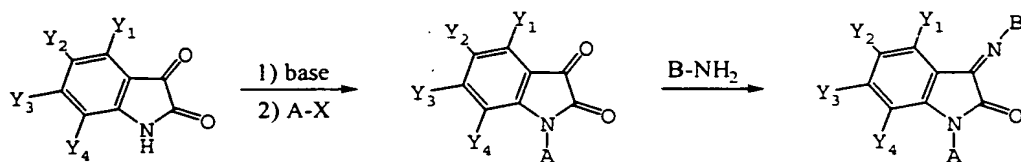
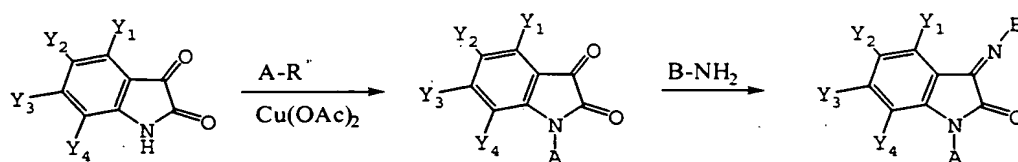
10 Example 311: (3Z)-3-[(3,4-DICHLOROPHENYL) IMINO]-1-(3-PYRIDINYLMETHYL)-1,3-DIHYDRO-2H-INDOL-2-ONE: Prepared by Procedures H (75 °C, 2 h), K (3-picoly chloride), and B. ESI-MS  $m/z$  383 (MH

15 Examples 91-114 and 254-311 as described above are merely illustrative of the methods used to synthesize indolone derivatives. Further derivatives may be obtained utilizing methods shown in Schemes 6a, 7a and 8-10. The substituents in Schemes 6a, 7a and 8-10 are described in the Detailed Description.

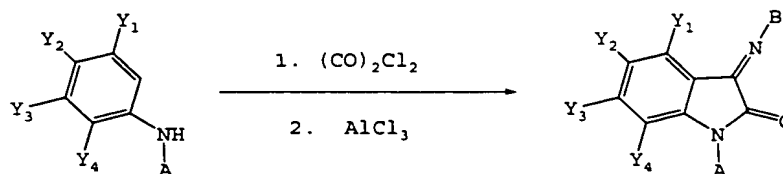
20

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form indolone derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

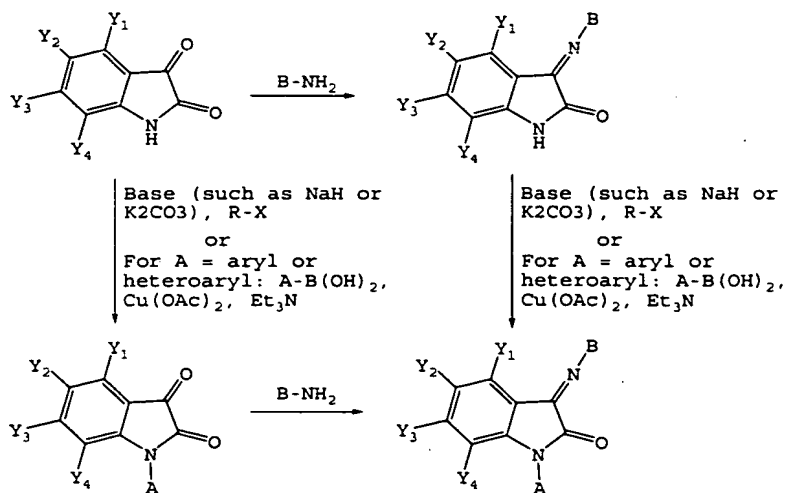
25

Scheme 6<sup>a</sup>Scheme 7<sup>a</sup>

<sup>a</sup> $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $A$ , and  $B$  are defined as described in the specification.  $X$  is a leaving group such as  $Cl$ ,  $Br$ ,  $I$ , or  $OTs$ .  $R$  is boric acid or a dialkylborate group.

Scheme 8<sup>a</sup>. Synthesis of Isatins

<sup>a</sup> $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $A$ , and  $B$  are defined as described in the specification.  
 $X$  is a leaving group such as  $Cl$ ,  $Br$ ,  $I$ , or  $OTs$ .  $R$  is boric acid or a dialkylborate group.

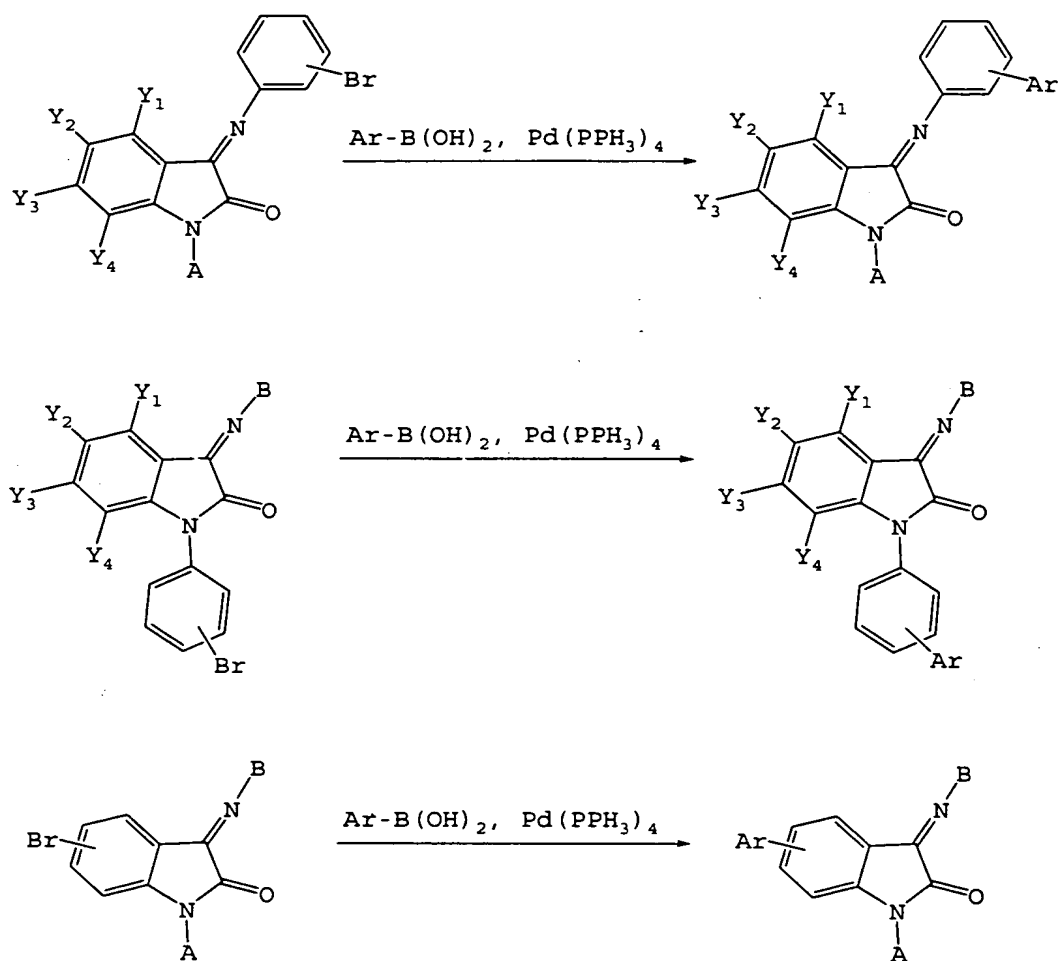
Scheme 9<sup>a</sup>. Synthesis of Substituted Iminoindolones

X is a leaving group such as a halogen or tosylate.

<sup>a</sup>Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, Y<sub>4</sub>, A, and B are defined as described in the specification.  
X is a leaving group such as Cl, Br, I, or OTs. R is boric acid or a dialkylborate group.



**Scheme 10<sup>a</sup>. Synthesis of Aryl or Heteroaryl-Substituted Iminoindolones**



<sup>a</sup> $\text{Y}_1, \text{Y}_2, \text{Y}_3, \text{Y}_4, \text{A}$ , and  $\text{B}$  are defined as described in the specification.  $\text{X}$  is a leaving group such as  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$ , or  $\text{OTs}$ .  $\text{R}$  is boric acid or a dialkylborate group.

Radioligand Binding of Indolones at Cloned Galanin Receptors

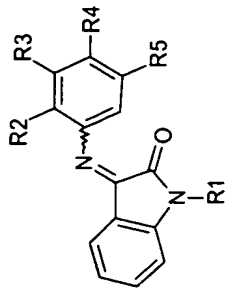
5 The binding properties of the indolones of the present invention were evaluated at the cloned human galanin receptors, GAL1, GAL2, and GAL3, using protocols described herein.

Radioligand Binding Assay Results

10 The indolones described in Examples 91-114 and 254-311 were assayed using cloned human galanin receptors. The compounds were found to be selective for the GAL3 receptor. The binding affinities of the compounds of Examples 91-114 and 254-311 are illustrated in Tables 4 and 4a.

15

Table 4. Binding Affinities of Indolones at Galanin Receptors.



Example	substitution					Ki (nM)		
	R1	R2	R3	R4	R5	GalR1	GalR2	GalR3
91	Ph	OMe	H	H	H	>10000	>10000	527
92	Ph	H	CF <sub>3</sub>	H	H	>10000	>10000	38
93	Ph	H	Me	H	H	>10000	>10000	171
94	Ph	H	Cl	H	H	>10000	>10000	49
95	Ph	H	H	CF <sub>3</sub>	H	>10000	>10000	29
96	Ph	H	H	Me	H	>10000	>10000	111
97	Ph	H	H	Cl	H	>10000	>10000	51
98	Ph	H	H	Br	H	>10000	>10000	38
99	Ph	H	H	F	H	>10000	>10000	229
100	Ph	H	H	OPh	H	>10000	>10000	90
101	Ph	H	H	OEt	H	>10000	>10000	305
102	Ph	H	H	OMe	H	>10000	>10000	429
103	Ph	H	Cl	H	Cl	>10000	>10000	68
104	Ph	H	Me	H	Me	>10000	>10000	143
105	allyl	H	Cl	Cl	H	>10000	>10000	97
106	allyl	H	Cl	H	Cl	>10000	>10000	62
107	isopropyl	H	H	Br	H	>10000	>10000	126

Key:            Ph= Phenyl            OMe= Methoxy            OEt= Ethoxy  
                 Me= Methyl            OPh= Phenoxy

Table 4a.

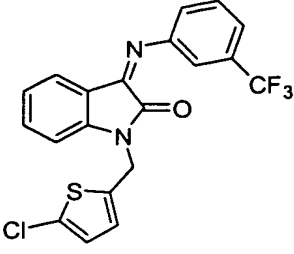
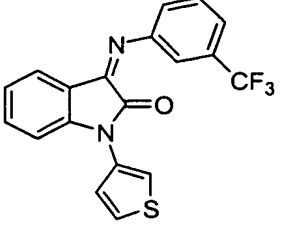
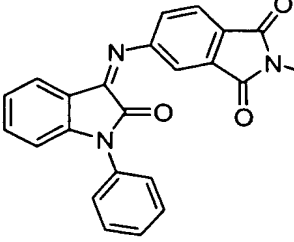
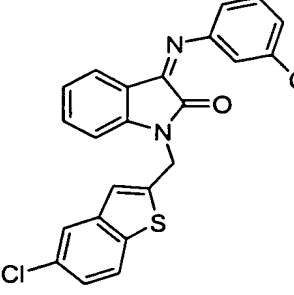
Example	Structure	Ki (nM) Gal3
108		84
109		103
110		138
111		1178

Table 4a.

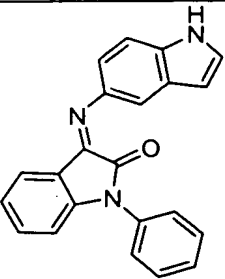
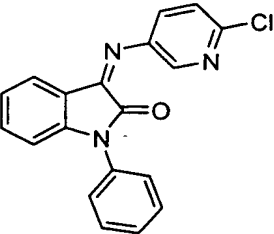
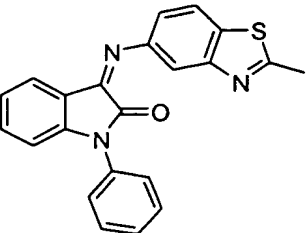
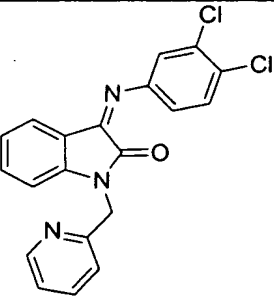
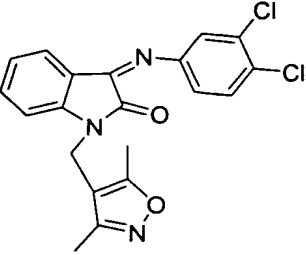
112		2324
113		136
114		569
254		64
255		49

Table 4a.

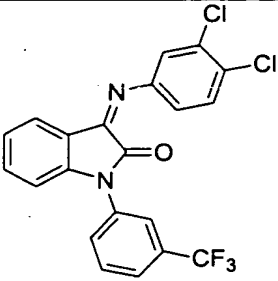
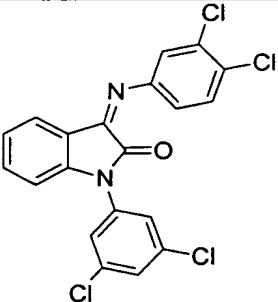
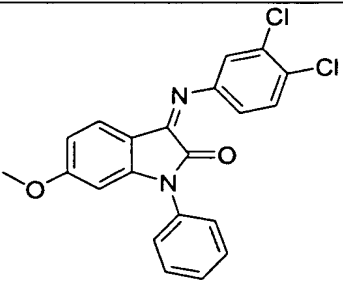
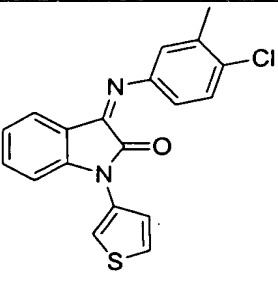
256		18
257		33
258		67
259		55

Table 4a.

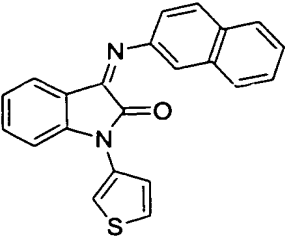
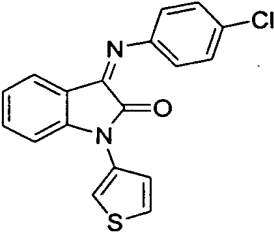
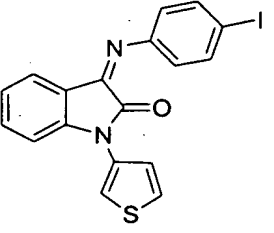
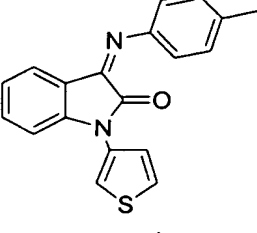
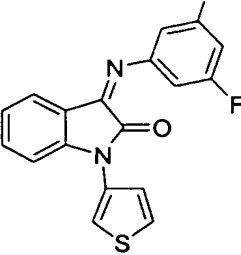
260		60
261		34
262		46
263		136
264		27

Table 4a.

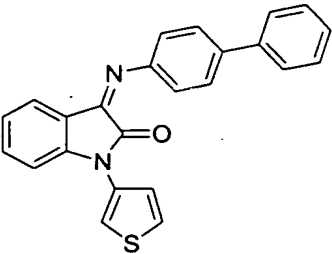
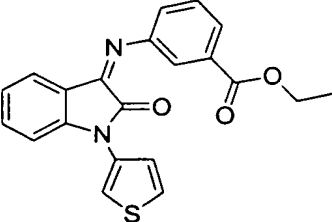
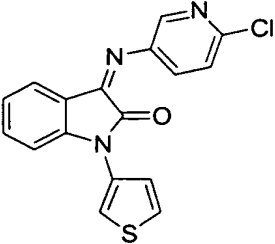
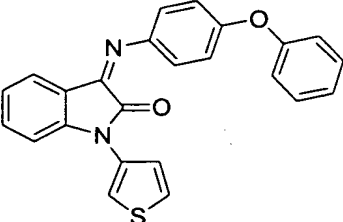
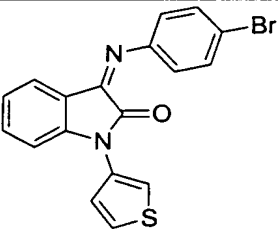
265		80
266		236
267		234
268		57
269		46



Table 4a.

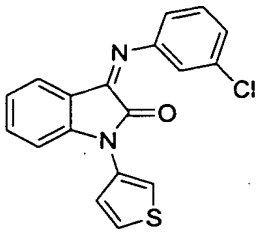
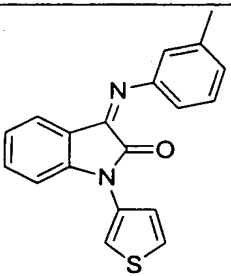
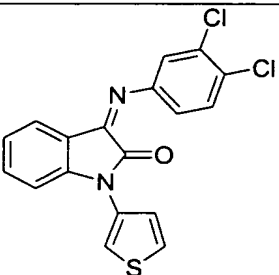
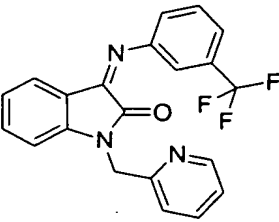
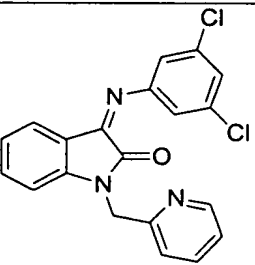
270		42
271		114
272		26
273		202
274		174

Table 4a.

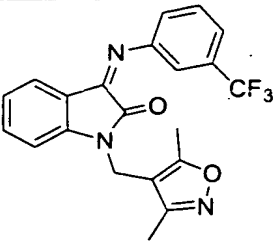
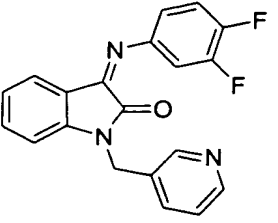
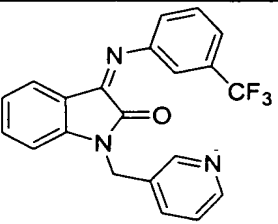
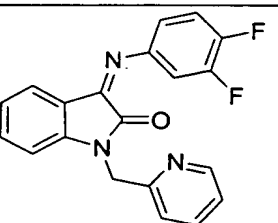
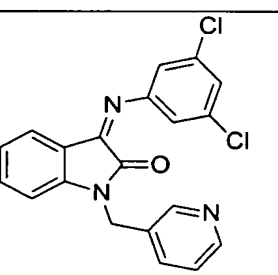
275		595
276		192
277		198
278		340
279		81

Table 4a.

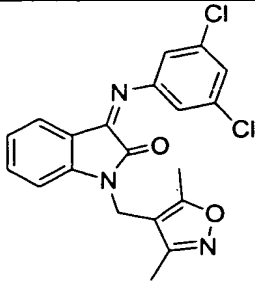
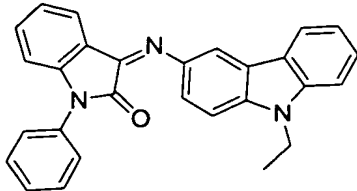
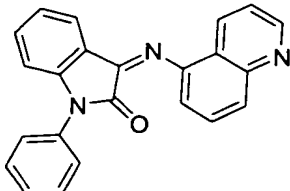
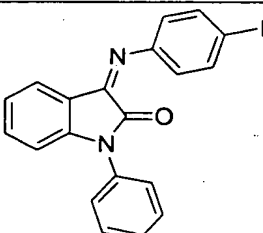
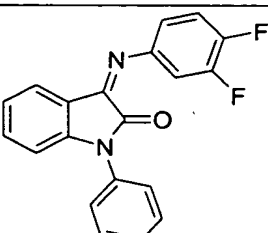
280		521
281		150
282		333
283		33
285		26

Table 4a.

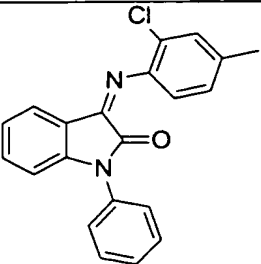
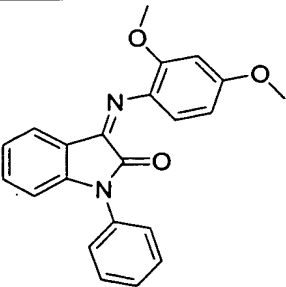
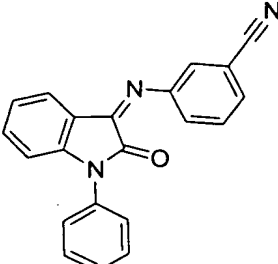
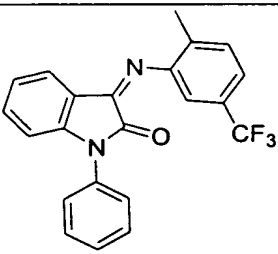
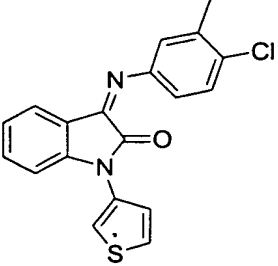
286		38
287		260
288		39
289		59
290		55

Table 4a.

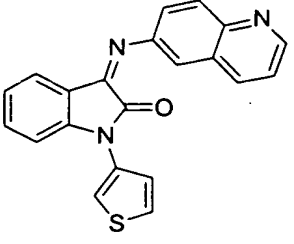
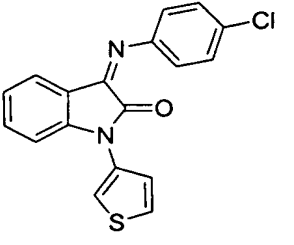
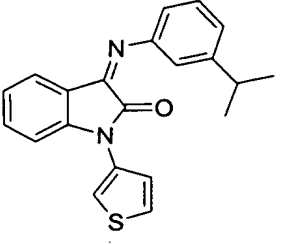
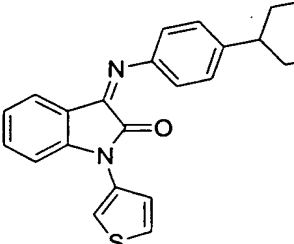
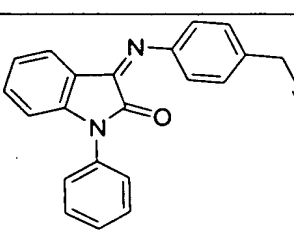
291		271
292		34
295		242
296		82
297		226

Table 4a.

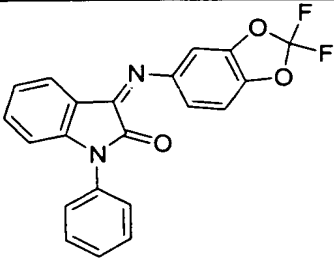
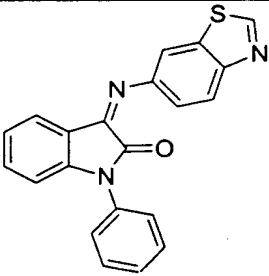
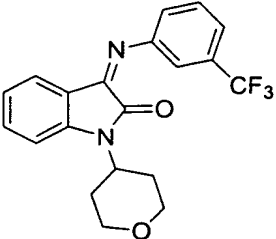
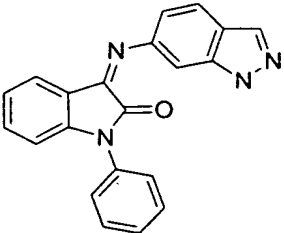
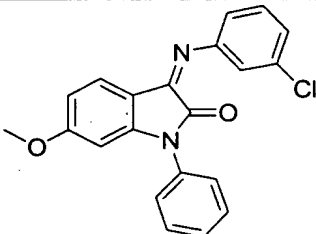
298		22
299		377
300		742
301		875
302		150

Table 4a.

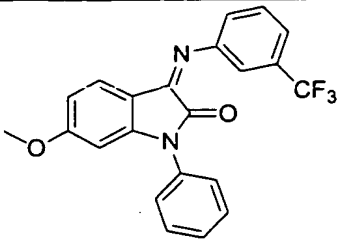
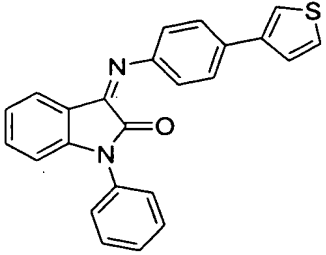
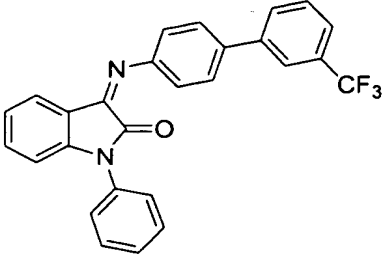
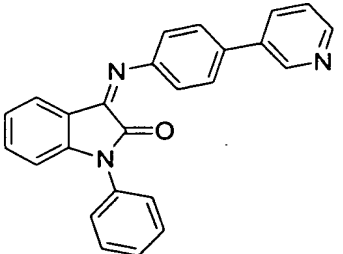
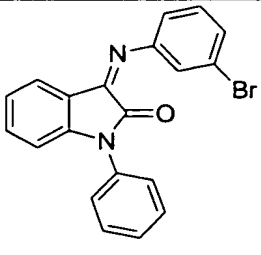
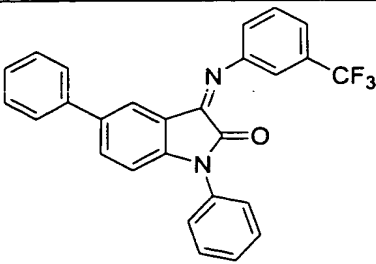
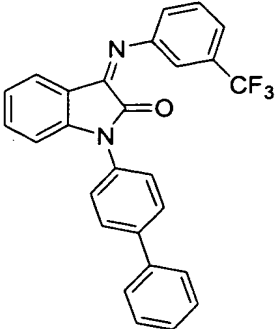
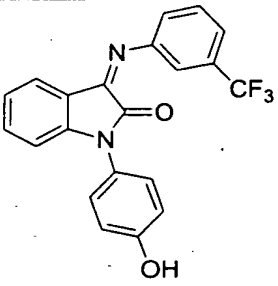
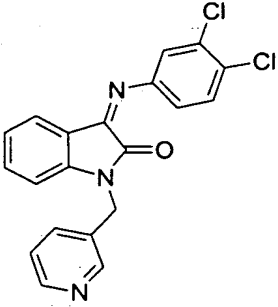
303		214
304		728
305		638
306		160
307		41

Table 4a.

308		98
309		224
310		126
311		32



### Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient  
5 finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

### I. In-Vivo Models

#### 10 A. Materials and Methods

##### 1. Forced Swim Test (FST)

The procedure used in this study was similar to that previously described (Porsolt, et al., 1978), except the  
15 water depth (30 cm in this procedure). The greater depth in this test prevented the rats from supporting themselves by touching the bottom of the cylinder with their feet. Swim sessions were conducted by placing rats in individual plexiglass cylinders (46 cm tall x 20 cm in  
20 diameter) containing 23-25°C water 30 cm deep (Porsolt, et al. used a depth of only 15 cm; also, see Detke, et al., 1995). Two swim tests were conducted always between 1200 and 1800 hours: an initial 15-min pretest followed 24 h later by a 5-minute test. Drug treatments were  
25 administered 60 minutes before the 5-minute test period. All other test sessions were conducted between 1300 to 1700 hours. Following all swim sessions, rats were removed from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes and returned to  
30 their home cages. All test sessions were videotaped using a Panasonic color video camera and recorder for scoring later.

Animals

Male Sprague-Dawley rats (Taconic Farms, NY) were used in all experiments. Rats were housed in pairs and maintained on a 12:12-h light-dark cycle. Rats were  
5 handled for 5 minutes each day for 5 days prior to behavioral testing.

Behavioral Scoring

The rat's behavior was rated at 5 second intervals during  
10 the 5 minute test as one of the following:

1. Immobility- rat remained floating in the water without  
struggling and was only making those movements  
necessary to keep its head above water;  
15
2. Climbing - rat was making active movements with its  
forepaws in and out of the water, usually directed  
against the walls;
- 20 3. Swimming - rat was making active swimming motions,  
more than necessary to merely maintain its head above  
water, e.g. moving around in the cylinder; and
4. Diving - entire body of the rat was submerged.

25 All of the behavior scoring was done by a single rater,  
who was blind to the treatment condition. The rater was  
also present in the room throughout the entire test  
period.

30

Drug Administration

Animals were randomly assigned to receive a single i.p.

administration of Example 92 (1, 3, 10 or 30 mg/kg, dissolved in 100% DMSO), fluoxetine (10 mg/kg, dissolved in distilled water) or vehicle (equal mixture of DMSO and distilled water) 30 minutes before the start of the 5 minute test period. All injections were given using 1 cc tuberculin syringe with 26 3/8 gauge needles (Becton-Dickinson, VWR Scientific, Bridgeport, NJ). The volume of injection was 1 ml/kg.

10 In another set of experiments, animals were randomly assigned to receive a single p.o. administration of one of the following treatments: Example 151 (1, 3 or 10 mg/kg), fluoxetine (5 or 10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start  
15 of the 5 minute test period. The drugs were dissolved in 100% N,N-dimethylacetamide. All administrations were given using 1 cc tuberculin syringes, to which a 3 inch, curved, stainless steel gavage needle was attached. The volume of administration was 1 ml/kg.

20

In other sets of experiments, animals were randomly assigned to receive a single p.o. administration of one of the following treatments: Example 103 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100%  
25 N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 272 (3 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 24 hours before the start of the 5 minute test period; or Example 98 (3, 10 and 30 mg/kg),  
30 fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 34 (0.3, 1, 3 and 10

mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of a 100% solution of dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 49 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period; or Example 22 (3, 10 and 30 mg/kg), fluoxetine (10 mg/kg) or vehicle (1 ml/kg of 100% N,N-dimethylacetamide) 60 minutes before the start of the 5 minute test period. The compounds were dissolved in 100% N,N-dimethylacetamide. All administrations were given using 1 cc tuberculin syringes, to which a 3 inch, curved, stainless steel gavage needle was attached. The volume of administration was 1 ml/kg.

15

The effect of 5 or 10 mg/kg of fluoxetine was utilized in the FST as a positive control.

#### Data Analysis

20 The forced swim test data (immobility, swimming, climbing, diving) were subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Student-Newman-Keuls test. The data were analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, MD, 1997). All data are presented as means  $\pm$  S.E.M.

#### 2. Social Interaction Test (SIT)

30 Rats were allowed to acclimate to the animal care facility for 5 days and were housed singly for 5 days prior to testing. Animals were handled for 5 minutes per day. The design and procedure for the Social Interaction

Test was carried out as previously described by Kennett, et al. (1997). On the test day, weight matched pairs of rats ( $\pm 5\%$ ), unfamiliar to each other, were given identical treatments and returned to their home cages.

5 Animals were randomly divided into 5 treatment groups, with 5 pairs per group, and were given one of the following i.p. treatments: Example 92 (10, 30 or 100 mg/kg), vehicle (1 ml/kg) or chlordiazepoxide (5 mg/kg). Dosing was 1 hour prior to testing. Rats were

10 subsequently placed in a white perspex test box or arena (54 x 37 x 26 cm), whose floor was divided up into 24 equal squares, for 15 minutes. An air conditioner was used to generate background noise and to keep the room at approximately 74°F. All sessions were videotaped using a

15 JVC camcorder (model GR-SZ1, Elmwood Park, NJ) with either TDK (HG ultimate brand) or Sony 30 minute videocassettes. All sessions were conducted between 1:00 - 4:30 P.M. Active social interaction, defined as grooming, sniffing, biting, boxing, wrestling, following

20 and crawling over or under, was scored using a stopwatch (Sportsline model no. 226, 1/100 sec. discriminability). The number of episodes of rearing (animal completely raises up its body on its hind limbs), grooming (licking, biting, scratching of body), and face washing (i.e. hands

25 are moved repeatedly over face), and number of squares crossed were scored. Passive social interaction (animals are lying beside or on top of each other) was not scored. All behaviors were assessed later by an observer who was blind as to the treatment of each pair. At the end of

30 each test, the box was thoroughly wiped with moistened paper towels.

### Animals

Male albino Sprague-Dawley rats (Taconic Farms, NY) were housed in pairs under a 12 hr light dark cycle (lights on at 0700 hrs.) with free access to food and water.

5

### Drug Administration

Example 92 was dissolved in 100% DMSO (Sigma Chemical Co., St. Louis, MO). Chlordiazepoxide (purchased from Sigma Chemical Co., St. Louis, MO) was dissolved in double distilled water. The vehicle consisted of 50% DMSO (v/v). All drug solutions were made up 10 minutes prior to injection and the solutions were discarded.

Example 34 was dissolved in 5% lactic acid, v/v. The vehicle consisted of 100% dimethylacetamide (DMA) and this was used to make up all drug solutions. All drug solutions were made up fresh each day and any unused solutions were discarded at the end of the test day. The volume of drug solution administered was 1 ml/kg.

20

### Data Analysis

The social interaction data (time interacting, rearing and squares crossed) were subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Student-Newman-Keuls test. The data were subjected to a test of normality (Shapiro-Wilk test). The data were analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, MD, 1997). All data are presented as means  $\pm$  S.E.M.

30

## B. Results

### 1. Forced Swim Test

#### A. The Effect Of Vehicle, Fluoxetine and Example 92 On 5 Immobility, Climbing and Swimming In The Forced Swim Test

##### Immobility

Statistical analysis indicated that there was a significant drug effect [ $F(4,45) = 12.1$ ,  $p < 0.0001$ ] on  
10 immobility. Subsequent post hoc analysis revealed that a single injection of 10 mg/kg i.p. of fluoxetine significantly decreased immobility to  $21.0 \pm 0.9$   
.. (Student-Newman-Keuls value was 36.5,  $p < 0.01$ ) compared to vehicle-treated controls (Table 5 and Figure 1). In  
15 addition, a single injection of either 3 or 10 mg/kg i.p. of Example 92 significantly decreased immobility ( $24 \pm 1.1$  &  $24 \pm 0.8$  counts at each dose, respectively) compared to vehicle-treated controls  $30 \pm 1.2$  (Student-Newman-Keuls values of 16.8 and 15.7, respectively)  
20 (Table 5 and Figure 1). No significant effects on immobility were observed with Example 92 at 30 mg/kg i.p. (Table 5 and Figure 1).

##### Climbing

25 The statistical analysis of the climbing counts indicated that there was a significant drug effect [ $F(4,45) = 4.4$ ,  $p = 0.004$ ]. Post hoc analysis indicated that a single injection of 10 mg/kg of fluoxetine did not significantly alter climbing counts compared to vehicle-treated animals  
30 (Table 5 and Figure 2). In contrast, a single injection of 10 mg/kg of Example 92 produced a significant increase ( $16.8 \pm 0.6$ ) in climbing counts (Student-Newman-Keuls value = 11.6,  $p < 0.01$ ) compared to vehicle-treated

animals ( $12 \pm 0.8$ ). Example 92 dosed at 1, 3 & 30 mg/kg did not significantly alter climbing.

#### Swimming

5 The statistical analysis of the swimming data indicated that there was a significant drug effect [ $F(4,45) = 6.6$ ,  $p < 0.0001$ ] (Table 5 and Figure 3). The post hoc test showed that a single injection of 10 mg/kg i.p. of fluoxetine produced a significant increase ( $25 \pm 1.2$ ) in  
10 swimming counts over the vehicle treated animals,  $18 \pm 1$  (Student-Newman-Keuls value of 19.9,  $p < 0.01$ ). In contrast, a single injection of 1, 3 or 10 mg/kg i.p. of Example 92 did not significantly alter swimming counts 20  
15  $\pm 1.1$ ,  $21 \pm 0.9$ , &  $18 \pm 0.9$ , respectively (Table 5 and Figure 3). (However, at 30 mg/kg i.p. Example 92 significantly increased swim behavior in the rat, comparable to fluoxetine at 10 mg/kg i.p. ( $27 \pm 2.5$  vs.  $25 \pm 1.2$ , Table 5 and Figure 3).

#### 20 Diving

This behavior was rarely observed following a single injection of vehicle ( $0.1 \pm 0.1$ , one animal dove once), fluoxetine ( $0.1 \pm 0.1$ , one animal out of 10 dove once), 1 mg/kg of Example 92 ( $0.6 \pm 0.2$ ; 5 animals had counts of  
25 2, 1, 1, 1, and 1), 3 mg/kg of Example 92 ( $0.6 \pm 0.3$ ; 3 animals had counts of 3, 2 and 1) or 10 mg/kg of Example 92 ( $0.5 \pm 0.5$ ; note: only one animal at this dose showed diving behavior and the score was 5). At 30 mg/kg i.p. of Example 92 diving behavior was only observed in two  
30 animals (mean =  $0.2 \pm 0.2$ ). Thus there was no significant drug effect on diving [ $F(4,45) = 0.77$ ,  $p = 0.55$ ].



**Table 5.** The effect of a single injection of vehicle, fluoxetine and Example 92 on immobility, climbing and swimming in the rat Forced Swim Test.

5 Treatment Dose (mg/kg) Immobility Climbing Swimming

Vehicle	-----	30 ± 1.2	12.0 ± 0.8	18 ± 1
Fluoxetine	10	21 ± 0.9 <sup>a</sup>	14.3 ± 0.9	25 ± 1.2 <sup>b</sup>
Example 92	1	28 ± 1.0	11.7 ± 1.1	20 ± 1.1
Example 92	3	24 ± 1.1 <sup>a</sup>	14.6 ± 1.5	21 ± 0.9
Example 92	10	24 ± 0.8 <sup>a</sup>	16.8 ± 0.6 <sup>c</sup>	18 ± 0.9
Example 92	30	25 ± 3.5	8.6 ± 1.7	27 ± 2.5 <sup>d</sup>

Each value represents the mean number of counts per 5 seconds ± S.E.M in a 5 minute observation period.

<sup>a</sup> Significantly less than Vehicle on immobility scores, p < 0.01, ANOVA and Student-Newman-Keuls test.

<sup>b</sup> Significantly greater than Vehicle and 1, 3 & 10 of Example 92, on swim scores, p < 0.01, ANOVA and Student-Newman-Keuls.

<sup>c</sup> Significantly greater than vehicle and 1, 3 & 30 mg/kg dose of Example 92 on climbing scores, p < 0.01, ANOVA and Student-Newman-Keuls

<sup>d</sup> Significantly greater than Vehicle, 1, 3 and 10 mg/kg i.p. of Example 92 on swim scores, p < 0.01, ANOVA and Student-Newman-Keuls test.

The results of the Forced Swim Test indicate that using a modified version of the Lucki forced swim test, a single injection of 10 mg/kg i.p. of fluoxetine produced a significant decrease in immobility and an increase in swimming in male Sprague-Dawley rats. This is consistent with findings from previous studies using the Lucki version (Detke, et al., 1995; Kirby and Lucki, 1997; Lucki, 1997; Page, et al., 1999; Reneric and Lucki, 1998). In addition, the results obtained using fluoxetine are consistent with those using other SSRIs (Detke, et al., 1995). Thus, a modified version of the Lucki forced swim test can consistently detect the antidepressant action of SSRIs such as fluoxetine.

Interestingly, at doses of 3 and 10 mg/kg i.p., Example 92, significantly decreased immobility compared to vehicle-treated animals. The magnitude of the decrease was not significantly different than that of fluoxetine. Thus, based on past interpretations of the Forced Swim Test, our results suggest that Example 92 has antidepressant-like properties.

A single injection of either 1, 3 or 10 mg/kg i.p. of Example 92 did not significantly alter swimming behavior. This is in contrast to the results obtained with fluoxetine, which increased swimming at 10 mg/kg i.p. Previously, it has been reported that compounds which selectively block serotonin uptake significantly increase swimming but not climbing whereas selective NE uptake blockers significantly increase climbing but not swimming behavior (Reneric and Lucki, 1998). Thus, the present

findings suggest that Example 92 exhibits a profile similar to NE and selective serotonin reuptake inhibitors (SSRIs) depending on the dose tested.

5 Finally, as previously reported by Lucki, diving behavior was rarely observed in vehicle or fluoxetine-treated animals (1 dive in one rat for each group). Example 92 at all doses tested did not produce a significant effect on diving behavior. It is possible that antidepressant  
10 drugs do not induce diving behavior.

In conclusion, compared to vehicle-treated animals, Example 92, at doses of 3 and 10 mg/kg, produced a significant decrease in immobility and a significant  
15 increase in climbing at the 10 mg/kg dose. At 30mg/kg i.p. Example 92 produced a significant increase in swimming behavior comparable with that observed with the antidepressant fluoxetine, thus supporting the antidepressant-like profile of Example 92.

20

B. The effect of Example 151, fluoxetine, and vehicle on swimming, climbing, immobility, and diving in the forced swim test.

25 Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA,  $F(5,46) = 3.5$ ,  $p = 0.0095$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly  
30 decreased immobility (Fisher's LSD value of 2.9) compared to vehicle-treated animals (Table 5a). In contrast, a single p.o. administration of 5 mg/kg of fluoxetine did

not significantly alter immobility compared to vehicle-treated animals.

A single p.o. administration of 1 mg/kg of Example 151  
5 did not significantly alter immobility compared to  
vehicle-treated animals (Table 5a). In contrast, a  
single p.o. administration of either 3 or 10 mg/kg of  
Example 151 significantly decreased immobility compared  
10 to animals treated with vehicle (Fisher's LSD values of  
2.8 and 2.6, respectively) or 5 mg/kg p.o. of fluoxetine  
(Fisher's LSD values of 2.6 and 2.4, respectively).  
There was no significant difference in the reduction in  
immobility between 10 mg/kg of fluoxetine and 3 and 10  
mg/kg of Example 151.

15

#### Swimming

Statistical analysis indicated a significant treatment  
effect on swimming behavior (ANOVA,  $F(5,46) = 5.5$ ,  $p = 0.0005$ ).  
Post hoc analyses revealed that a single p.o.  
20 administration of 10 mg/kg of fluoxetine produced a  
significant increase in swimming behavior compared to  
vehicle-treated animals (Student-Newman-Keuls value of  
16.8 (Table 5a). In contrast, a single p.o.  
administration of 5 mg/kg of fluoxetine did not  
25 significantly alter swimming compared to vehicle-treated  
animals.

A single p.o. administration of either 1, 3 or 10 mg/kg  
of Example 151 significantly increased swimming (Student-  
30 Newman-Keuls values of 6.9, 14.8 and 13.4, respectively)  
compared to vehicle-treated animals. There was no  
significant difference in the magnitude of the increase

in swimming between the doses of Example 151. The 3 and 10 mg/kg doses of Example 151 produced a significantly greater increase in swimming compared to animals treated with 5 mg/kg p.o. of fluoxetine. There was no significant difference in the increase in swimming between animals treated with 10 mg/kg of fluoxetine and those treated with Example 151.

#### Climbing behavior

Statistical analysis revealed that climbing was not significantly altered by a single p.o administration of 1, 3 or 10 mg/kg of Example 151 or 5 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(5,46) = 0.81$ ,  $p = 0.55$ ) (Table 5a).

#### Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 1, 3 or 10 mg/kg of Example 151 or 5 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(5,46) = 0.36$ ,  $p = 0.87$ ) (Table 5a).

TABLE 5a. The effect of a single p.o. administration of vehicle, 1, 3 and 10 mg/kg of Example 151 and 5 and 10 mg/kg of fluoxetine on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

<u>Treatment</u>	<u>Immobility</u>	<u>Climbing</u>	<u>Swimming</u>	<u>Diving</u>
Vehicle	46 ± 1.8	2.7 ± 0.7	11.4 ± 1.2	0.4 ± 0.4
1 mg/kg EX151	41 ± 2.0	2.3 ± 0.6	16.8 ± 1.4 <sup>d</sup>	0.2 ± 0.2
3 mg/kg EX151	38 ± 2.0 <sup>a</sup>	2.4 ± 0.5	19.5 ± 1.5 <sup>e</sup>	0.3 ± 0.2
10 mg/kg EX151	39 ± 1.8 <sup>b</sup>	2.2 ± 0.5	18.9 ± 1.5 <sup>e</sup>	0.3 ± 0.2
5 mg/kg Fluox	45 ± 1.3 <sup>c</sup>	1.2 ± 0.4	13.9 ± 1.0	0.0 ± 0.0
10 mg/kg Fluox	38 ± 2.3 <sup>a</sup>	2.0 ± 0.6	19.8 ± 1.8 <sup>e</sup>	0.6 ± 0.6

Each value represents the mean ± S.E.M. A total of 8-9 animals were examined for each treatment group. Fluox = Fluoxetine, EX151 = Example 151. Experiments were conducted 1 hr. after the appropriate treatment.

<sup>a</sup>Significantly less than Vehicle (p < 0.01), ANOVA and Fisher's protected t test.

<sup>b</sup>Significantly less than Vehicle (p < 0.05), ANOVA and Fisher's protected t test.

<sup>c</sup>Significantly greater than 3 and 10 mg/kg of Example 151 and 10 mg/kg of fluoxetine, ANOVA and ANOVA and Fisher's protected t test.

<sup>d</sup>Significantly greater than Vehicle ( $p < 0.05$ ) and 5 mg/kg of fluoxetine ( $p < 0.05$ ), ANOVA and Student-Newman-Keuls test.

5   <sup>e</sup>Significantly greater than Vehicle ( $p < 0.01$ ) and 5 mg/kg of fluoxetine ( $p < 0.05$ ), ANOVA and Student-Newman-Keuls test.

The results of this study indicate that a single p.o. administration of Example 151, at doses of 1, 3 and 10 mg/kg, produces a significant increase in swimming behavior. There was no significant difference in the magnitude of the increase in swimming between the doses of Example 151, although the 1 mg/kg dose produced a lower increase. In contrast, only the 3 and 10 mg/kg doses of Example 151 significantly decreased immobility compared to vehicle-treated animals. Thus, it appears that a single p.o. administration of either 3 or 10 mg/kg, compared to 1 mg/kg of Example 151, produce a more robust antidepressant profile in the FST in male Sprague-Dawley rats. Our results also indicate that Example 151 produced changes in swimming and immobility that were not significantly different from that of 10 mg/kg p.o. of fluoxetine. This suggests that Example 151 produces behavioral effects similar to that of 10 mg/kg of fluoxetine in the FST.

A single p.o. administration of 5 mg/kg of fluoxetine did not significantly alter swimming, climbing, diving or immobility compared to vehicle treated animals. This finding, together with the data indicating that 10 mg/kg of fluoxetine produces a significant effect on swimming

and immobility in the FST, suggest that the threshold dose of fluoxetine is greater than 5, but less than 10 mg/kg. This is consistent with ex vivo data indicating that a p.o. dose of 7 mg/kg of fluoxetine is required to  
5 inhibit 5-HT uptake in the CNS by 50% (Leonard, 1996).

In conclusion, the results of this study indicate that a single p.o. administration of Example 151 (particularly the 3 and 10 mg/kg doses) produces behavioral effects in  
10 the FST in rats that resemble those of antidepressants.

**C. The Effect of a Single P.O. Administration of Example 103, Fluoxetine and Vehicle on Swimming, Immobility, Climbing and Diving in the Forced Swim Test**

15

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA,  $F(4,40) = 6.3$ ,  $p = 0.0005$ ). Post hoc analyses revealed that a single p.o.  
20 administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 8.3) compared to vehicle-treated animals (Table 5b). The decrease in immobility produced by fluoxetine was significantly greater than that of either 3 or 10 mg/kg  
25 p.o. of Example 103 (Student-Newman-Keuls values of 9.1 and 6.1, respectively).

A single p.o. administration of either 3 or 10 mg/kg of Example 103 did not significantly alter immobility  
30 compared to vehicle-treated animals. However, the 30 mg/kg dose of Example 103 produced a significant decrease in immobility (Student-Newman-Keuls values of 13.9)



compared to vehicle-treated animals. In addition, the decrease in immobility produced by 30 mg/kg of Example 103 was significantly greater than that of 3 and 10 mg/kg of Example 103 (Student-Newman-Keuls values of 14.4 and 10.6, respectively). There was no significant difference between fluoxetine and 30 mg/kg of Example 103 in the reduction of immobility.

#### Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA,  $F(4,40) = 9.2$ ,  $p < 0.0001$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to animals treated with vehicle, 3 or 10 mg/kg p.o. of Example 103 (Student-Newman-Keuls values of 14.9, 15.3 and 11.6, respectively) (Table 5b).

A single p.o. administration of either 3 or 10 mg/kg of Example 103 did not significantly alter swimming behavior compared to vehicle-treated animals. A single p.o. administration of 30 mg/kg of Example 103 produced a significantly greater increase in swimming behavior compared to animals treated with either vehicle, 3 or 10 mg/kg of Example 103 (Student-Newman-Keuls values of 18, 18.6 and 14.5 respectively).

#### Climbing behavior

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 103 or 10 mg/kg of

fluoxetine compared to vehicle-treated animals (ANOVA,  $F(4,40) = 1.2$ ,  $p = 0.31$ ) (Table 5b).

#### Diving

- 5 Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 103 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(4,40) = 1.1$ ,  $p = 0.36$ ) (Table 5b).

TABLE 5b. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 103 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

5

<u>Treatment</u>	<u>Immobility</u>	<u>Climbing</u>	<u>Swimming</u>	<u>Diving</u>
Vehicle	44 ± 1.7	2.9 ± 0.7	13.1 ± 1.2	0.4 ± 0.2
3 mg/kg EX103	44 ± 2.7	2.8 ± 0.6	13.2 ± 1.9	0.5 ± 0.4
10 mg/kg EX103	42 ± 2.2	3.5 ± 0.6	14.3 ± 1.6	0.4 ± 0.2
30mg/kg EX103	32 ± 1.8 <sup>a</sup>	4.8 ± 0.7	22.7 ± 1.1 <sup>c</sup>	1.1 ± 0.5
10 mg/kg Fluox	34 ± 2.3 <sup>b</sup>	3.8 ± 0.8	21.8 ± 1.4 <sup>c</sup>	0.1 ± 0.1

Each value represents the mean ± S.E.M. A total of 8-10 animals were examined for each treatment group. Fluox =  
 10 Fluoxetine, EX103 = Example 103. Experiments were conducted 1 hr. after the appropriate treatment.

<sup>a</sup>Significantly less than Vehicle, 3 and 10 mg/kg of  
 15 Example 103,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>b</sup>Significantly less than Vehicle, 3 and 10 mg/kg of  
 Example 103,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

20

<sup>c</sup>Significantly greater than Vehicle, 3 and 10 mg/kg of Example 103,  $P < 0.01$ , ANOVA and Student-Newman-Keuls test.

5 The results of this study indicated that as previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility in male rats in the FST compared to vehicle-treated animals. The  
10 magnitude of these changes are similar to those reported of our past studies with 10 mg/kg p.o. of fluoxetine. In contrast, neither climbing nor diving behavior was significantly altered by a single p.o. administration of 10 mg/kg of fluoxetine.

15

A single p.o. administration of either 3 or 10 mg/kg of Example 103 did not significantly alter swimming, climbing, immobility or diving in male rats in the FST, indicating that at these doses using the p.o. route,  
20 Example 103 does not exhibit antidepressant action in the FST. In contrast, a single p.o. administration of 30 mg/kg of Example 103 produced a significant increase in swimming and a significant decrease in immobility compared to animals treated with vehicle or 10 mg/kg of  
25 Example 103. However, the 30 mg/kg p.o. dose of Example 103 did not significantly alter diving or climbing counts compared to vehicle-treated animals. The increase in swimming counts produced by 30 mg/kg p.o. of Example 103 was comparable to that for 10 mg/kg of fluoxetine.

30

In conclusion, a single p.o. administration of 30 mg/kg of Example 103 (one hour before the last swim test)

increases swimming and decreases immobility counts in the FST, suggesting that Example 103 has antidepressant properties.

5 D. Effect of a single p.o. administration of Example 272, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test

Immobility

10 Statistical analysis indicated a significant effect of treatment on immobility (ANOVA,  $F(2,27) = 5.2$ ,  $p = 0.0126$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine and 3 mg/kg of Example 272 significantly decreased immobility (Student-  
15 Newman-Keuls values of 5.4 and 9.8, respectively) compared to vehicle-treated animals (Table 5c). There was no significant difference between fluoxetine and 3 mg/kg of Example 272 in the reduction of immobility (Student-Newman-Keuls value of 0.53).

20

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA,  $F(2,27) = 9.9$ ,  $p < 0.0007$ ). Post hoc analyses revealed that a single p.o.  
25 administration of 10 mg/kg of fluoxetine and Example 272 produced a significant increase in swimming behavior compared to animals treated with vehicle (Student-Newman-Keuls values of 11.9 and 17.5, respectively) (Table 5c). There was no significant difference in the  
30 increase in swimming between 10 mg/kg of fluoxetine and 3 mg/kg of Example 272 (Student-Newman-Keuls value of 0.42).

Climbing behavior

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of either 3 mg/kg of Example 272 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(2,27) = 1.8$ ,  $p = 0.19$ ) (Table 5c).

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3 mg/kg of Example 272 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(2,27) = 0.65$ ,  $p = 0.53$ ) (Table 5c).

TABLE 5c. The effect of a single p.o. administration of vehicle, fluoxetine and Example 272 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

5

<u>Treatment</u>	<u>Immobility</u>	<u>Climbing</u>	<u>Swimming</u>	<u>Diving</u>
Vehicle	43 ± 3.3	2.4 ± 0.4	13.4 ± 2.2	0.2 ± 0.1
3 mg/kg EX272	33 ± 1.8 <sup>a</sup>	3.9 ± 0.6	22.9 ± 1.3 <sup>b</sup>	0.6 ± 0.4
10 mg/kg FLUOX	35 ± 1.7 <sup>a</sup>	3.3 ± 0.6	21.4 ± 1.0 <sup>b</sup>	0.2 ± 0.1

Each value represents the mean ± S.E.M. A total of 9-10 animals were examined for each treatment group.

10 Abbreviations: FLUOX = Fluoxetine, EX272 = Example 272. Animals received 1 p.o. administration of the appropriate treatment 24 hours before the test day.

<sup>a</sup>Significantly less than Vehicle,  $p < 0.05$ , ANOVA and  
15 Student-Newman-Keuls test.

<sup>b</sup>Significantly less than Vehicle,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

The finding of this study indicate that a single p.o.  
20 administration of 3 mg/kg of the compound Example 272 produced a significant increase in swimming and a significant decrease in immobility 24 hours after administration compared to vehicle-treated animals. However, the administration of Example 272 did not  
25 significantly alter climbing or diving compared to

vehicle-treated animals. These results are similar to those of a single p.o. administration of 10 mg/kg of fluoxetine. Our finding suggest that a single p.o. administration of 3 mg/kg of Example 272 has the profile of an antidepressant in male Sprague-Dawley rats in the Lucki version of the FST.

E. Effect of a single p.o. administration of Example 98, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test.

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA,  $F(4,43) = 7.5$ ,  $p = 0.0001$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 23.8) compared to vehicle-treated animals (Table 5d).

A single p.o. administration of 3, 10 or 30 mg/kg of Example 98 significantly decreased immobility compared to vehicle-treated animals (Student-Newman-Keuls values of 19.3, 9.7 and 13.7, respectively). There was no significant difference between fluoxetine and 3, 10 or 30 mg/kg of Example 98 in the magnitude of the reduction of immobility. There were no significant differences between the doses of Example 98 regarding the magnitude of the decrease in immobility.

Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA,  $F(4,43) = 11$ ,  $p <$



0.0001). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to vehicle-treated animals (Student-Newman-Keuls value of 35.1) (Table 5d).

A single p.o. administration of 3, 10 or 30 mg/kg of Example 98 significantly increased swimming compared to vehicle-treated animals (Student-Newman-Keuls values of 24.4, 14.7 and 25.1, respectively) (Table 5d). There was no significant difference between fluoxetine and 3, 10 or 30 mg/kg of Example 98 in the magnitude of the increase in swimming. There were no significant differences between the doses of Example 98 regarding the magnitude of the increase in immobility.

#### Climbing behavior

There was a significant treatment effect on climbing behavior (ANOVA,  $F(4,43) = 2.8$ ,  $p = 0.04$ ) (Table 5d). Post hoc tests indicated that this was the result of the 3 mg/kg dose of Example 98 producing a significantly greater increase in climbing compared to 30 mg/kg of Example 98 (Table 5d; Student-Newman-Keuls value of 8.6). There was no significant difference in the number of climbing counts between animals treated with vehicle and Example 98.

#### Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 98 or 10 mg/kg of fluoxetine

compared to vehicle-treated animals (ANOVA,  $F(4,43) = 1.29$ ,  $p = 0.29$ ) (Table 5d).

TABLE 5d. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 98 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

<u>Treatment</u>	<u>Immobility</u>	<u>Climbing</u>	<u>Swimming</u>	<u>Diving</u>
Vehicle	$48 \pm 1.2$	$2.5 \pm 0.5$	$8.8 \pm 0.9$	$0.4 \pm 0.3$
3 mg/kg EX98	$35 \pm 2.6^a$	$4.3 \pm 0.9^b$	$20.4 \pm 1.9^c$	$0.1 \pm 0.1$
10 mg/kg EX98	$39 \pm 1.1^a$	$2.4 \pm 0.3$	$17.6 \pm 1.0^c$	$0.8 \pm 0.4$
30 mg/kg EX98	$38 \pm 2.3^a$	$2.0 \pm 0.3$	$20.3 \pm 2.1^c$	$0.2 \pm 0.2$
10 mg/kg Fluox	$34 \pm 3.0^a$	$3.4 \pm 0.8$	$22.8 \pm 2.2^c$	$0.1 \pm 0.1$

Each value represents the mean  $\pm$  S.E.M. A total of 10 animals were examined for each treatment group, except for the fluoxetine and 3 mg/kg groups, where a total of 9 animals were examined. Vehicle = 100% DMA.

Fluox = Fluoxetine, EX98 = Example 98. Experiments were conducted 1 hr. after the appropriate treatment.

<sup>a</sup>Significantly less than Vehicle,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>b</sup>Significantly greater than 30 mg/kg of Example 98,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

5 <sup>c</sup>Significantly greater than Vehicle,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

The results of this study clearly indicate that in male Sprague-Dawley rats, a single p.o. administration of 3,  
10 10 or 30 mg/kg of Example 98 produces a significant increase in swimming and a significant decrease in immobility compared to vehicle-treated animals in the FST. In addition, the Example 98 induced alterations were similar in magnitude to that of a single p.o.  
15 administration of 10 mg/kg p.o. of fluoxetine. However, neither fluoxetine nor Example 98 produced a significant alteration in climbing or diving compared to vehicle-treated animals.

20 In conclusion, these results indicate that a single p.o. administration of Example 98 produces a profile in the modified Lucki version of the FST resembling that of the clinically established antidepressant fluoxetine.

25 F. Effect of a single p.o. administration of Example 34, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test.

#### Immobility

30 Statistical analysis indicated a significant effect of treatment on immobility (ANOVA,  $F(5,44) = 18.1$ ,  $p < 0.0001$ ). Post hoc analyses revealed that a single p.o.

administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 39.6) compared to vehicle-treated animals (Table 5e). Fluoxetine also produced a significantly greater decrease  
5 in immobility compared to the 0.3 and 10 mg/kg doses of Example 34 (Student-Newman-Keuls values of 15.3 and 29.8, respectively). There was no significant difference in the magnitude of the decrease in immobility between fluoxetine and the 1 and 3 mg/doses of Example 34.

10

A single p.o. administration of 0.3, 1 and 3 mg/kg of Example 34 significantly decreased immobility compared to vehicle-treated animals (Student-Newman-Keuls values of 7.03, 41.6 and 42.0, respectively) (Table 5e). However, a  
15 single p.o. administration of 10 mg/kg of Example 34 did not significantly decrease in immobility compared to vehicle-treated animals. The magnitude of the decrease in immobility produced by 1 and 3 mg/kg doses of Example 34 was significantly greater than that for the 0.3  
20 (Student-Newman-Keuls values of 14.5 and 15.3) and 10 mg/kg (Student-Newman-Keuls of 30.6 and 31.3, respectively) doses of Example 34 (Student-Newman-Keuls of 21.3 and 10.8, respectively).

25 Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA,  $F(5,44) = 33.0$ ,  $p < 0.0001$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a  
30 significant increase in swimming compared to animals treated with vehicle, 0.3 or 10 mg/kg of Example 34 (Student-Newman-Keuls values of 73.7, 30.0 and 53.9,

respectively) (Table 5e). There was no significant difference in swimming behavior between fluoxetine and the 1 and 3 mg/kg p.o. of Example 34.

- 5 A single p.o. administration of either 0.3, 1 or 3 mg/kg of Example 34 produced a significant increase in swimming behavior compared to vehicle-treated animals (Student-Newman-Keuls values of 12.1, 72.1 and 80.3, respectively) (Table 5e). In addition, the magnitude of the increase  
10 in swimming was greater for the 1 and 3 mg/kg doses (Student-Newman-Keuls values of 50.4 and 57.9, respectively) compared to 0.3 mg/kg of Example 34.

#### Climbing behavior

- 15 Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA,  $F(5,44) = 3.2$ ,  $p = 0.014$ ) (Table 5e). Post hoc analyses revealed that a single p.o. administration of 1 mg/kg of Example 34 produced a significant increase in climbing compared to  
20 vehicle-treated animals (Student-Newman-Keuls value of 9.2) (Table 5e)

#### Diving

- Statistical analysis revealed that diving was not  
25 significantly altered by a single p.o. administration of 0.3, 1, 3 or 10 mg/kg of Example 34 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(5,44) = 0.75$ ,  $p = 0.59$ ) (Table 5e).

TABLE 5e. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and Example 34 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

5

Treatment      Immobility      Climbing      Swimming      Diving

Vehicle	52 ± 1.3	2.1 ± 0.6	6.0 ± 0.6	0.8 ± 0.7
0.3 mg/kg EX34	45 ± 1.5 <sup>a</sup>	3.3 ± 0.7	11.6 ± 0.9 <sup>d</sup>	0.2 ± 0.1
1 mg/kg EX34	35 ± 1.9 <sup>b</sup>	5.0 ± 0.8 <sup>c</sup>	19.6 ± 1.3 <sup>d,e</sup>	0.3 ± 0.2
3 mg/kg EX34	35 ± 2.0 <sup>b</sup>	4.3 ± 0.8	20.8 ± 1.3 <sup>d,e</sup>	0.3 ± 0.3
10 mg/kg EX34	49 ± 1.4	2.0 ± 0.4	8.2 ± 1.2	0.4 ± 0.3
10 mg/kg Fluox	34 ± 3.3 <sup>b</sup>	4.5 ± 1.2	21.3 ± 1.8 <sup>d,e</sup>	1.0 ± 0.8

Each value represents the mean ± S.E.M. A total of 9 animals were examined for each treatment group, except for the 3 mg/kg Example 34 and fluoxetine groups, where a total of 8 and 6 animals were examined, respectively. Fluox = Fluoxetine, EX34 = Example 34. Experiments were conducted 1 hr. after the appropriate treatment.

15

<sup>a</sup>Significantly less than Vehicle,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>b</sup>Significantly less than Vehicle, 0.3 and 10 mg/kg of Example 34, ANOVA and Student-Newman-Keuls test.

<sup>c</sup>Significantly greater than Vehicle,  $p < 0.05$ , ANOVA and  
5 Student-Newman-Keuls test.

<sup>d</sup>Significantly greater than Vehicle ( $p < 0.01$ ) and 10 mg/kg Example 34 (all  $p < 0.01$  except for 0.3 mg/kg of Example 34,  $p < 0.05$ ), ANOVA and Student-Newman-Keuls  
10 test.

<sup>e</sup>Significantly greater 0.3 mg/kg of Example 34,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

15 The results of this study indicate that a single p.o. administration (one hour before the final swim test) of either 0.3, 1 or 3 mg/kg of Example 34 produced a significant increase in swimming and a significant decrease in immobility compared to vehicle-treated  
20 animals. However, a single p.o. administration of 10 mg/kg of Example 34 did not significantly alter swimming or climbing compared to vehicle-treated animals. Currently, the explanation for the lack of effect of 10 mg/kg p.o. of Example 34 is unknown. The 1 mg/kg dose of  
25 Example 34 produced a significant increase in climbing compared to vehicle-treated animals. The magnitude of the alterations in swimming and immobility produced by 1 and 3 mg/kg p.o. of Example 34 was significantly greater than that for the 0.3 and 10 mg/kg doses of Example 34.  
30 Finally, none of the doses of Example 34 significantly

altered diving behavior compared to vehicle-treated controls.

As previously reported, a single p.o. administration of  
5 10 mg/kg of fluoxetine produced a significant increase in  
swimming and a significant decrease in immobility  
compared to vehicle-treated controls. The effect of  
fluoxetine on swimming and immobility was similar to that  
for the 1 and 3 mg/kg doses of Example 34 but was  
10 significantly greater than that of 0.3 and 10 mg/kg of  
Example 34. A single p.o. administration of 10 mg/kg of  
fluoxetine did not significantly alter climbing or diving  
behavior compared to vehicle-treated controls.

15 In conclusion, these results indicate that a single p.o.  
administration of 0.3, 1 or 3 mg/kg Example 34 produces  
an effect in the FST that resembles that of  
antidepressants in male Sprague-Dawley rats.

20

G. Effect of a single p.o. administration of Example 49,  
fluoxetine and vehicle on swimming, climbing, immobility  
and diving in the forced swim test.

25 Immobility

Statistical analysis indicated a significant effect of  
treatment on immobility (ANOVA,  $F(4,41) = 6.5$ ,  $p =$   
0.0004). Post hoc analyses revealed that a single p.o.  
administration of 10 mg/kg of fluoxetine significantly  
30 decreased immobility (Student-Newman-Keuls value of 15.6)  
compared to vehicle-treated animals (Table 5f).



A single p.o. administration of either 3 or 10 mg/kg of Example 49 did not significantly alter immobility compared to vehicle-treated animals. However, the 30 mg/kg dose of Example 49 produced a significant decrease  
5 in immobility (Student-Newman-Keuls values of 8.0) compared to vehicle-treated animals. In addition, the decrease in immobility produced by either fluoxetine or 30 mg/kg of Example 49 was significantly greater than that of the 10 mg/kg dose of Example 49. There was no  
10 significant difference between fluoxetine and 30 mg/kg of Example 49 in the reduction of immobility.

#### Swimming

Statistical analysis indicated a significant treatment  
15 effect on swimming behavior (ANOVA,  $F(4,41) = 16.2$ ,  $p < 0.0001$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to animals treated with vehicle, 3, 10 or 30 mg/kg p.o. of  
20 Example 49 (Student-Newman-Keuls values of 42.7, 20.9, 47.5 and 8.4, respectively) (Table 5f).

A single p.o. administration of either 3 or 10 mg/kg of Example 49 did not significantly alter swimming behavior  
25 compared to vehicle-treated animals. A single p.o. administration of 30 mg/kg of Example 49 produced a significantly greater increase in swimming behavior compared to animals treated with vehicle, 3 or 10 mg/kg of Example 49 (Student-Newman-Keuls values of 14 and  
30 16.9, respectively).

Climbing behavior

There was a significant treatment effect on climbing behavior (ANOVA,  $F(4,42) = 5.9$ ,  $p = 0.007$ ). Post hoc tests indicated that this was the results of the vehicle, 3, 10 and 30 mg/kg doses of Example 49 producing a significantly greater increase in climbing counts compared to fluoxetine-treated animals (Table 5f; Student-Newman-Keuls values of 7.9, 18.1, 14.05 and 12.9, respectively). There was no significant difference in the number of climbing counts between animals treated with vehicle and Example 49.

Diving

Statistical analysis revealed that diving was not significantly altered by a single p.o. administration of 3, 10 or 30 mg/kg of Example 49 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(4,41) = 1.06$ ,  $p = 0.38$ ) (Table 5f).

TABLE 5f. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 49 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

5

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	47 ± 1.2	1.8 ± 0.3	10.6 ± 1.1	0.2 ± 0.2
3 mg/kg EX 49	43 ± 1.9	3.0 ± 0.7	13.1 ± 1.4	1.0 ± 0.7
10 mg/kg EX49	48 ± 1.7	2.4 ± 0.7	10.0 ± 1.0	0.0 ± 0.0
30 mg/kg EX49	41 ± 2.0 <sup>a</sup>	2.3 ± 0.4	16.7 ± 1.3 <sup>d</sup>	0.4 ± 0.4
10 mg/kg Fluox	38 ± 1.3 <sup>b</sup>	0.0 ± 0.0 <sup>c</sup>	21.6 ± 1.1 <sup>e</sup>	0.8 ± 0.5

Each value represents the mean ± S.E.M. A total of 10 animals were examined for each treatment group, except for the fluoxetine and 3 mg/kg groups, where a total of 9 and 7 animals were examined, respectively.

15

Fluox = Fluoxetine, EX49 = Example 49. Experiments were conducted 1 hr. after the appropriate treatment.

<sup>a</sup>Significantly less than Vehicle and 10 mg/kg of Example 49,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>b</sup>Significantly less than Vehicle and 10 mg/kg of Example 49,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

20

<sup>c</sup>Significantly less than all other treatment groups,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>d</sup>Significantly greater than vehicle and 10 mg/kg of Example 49,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>e</sup>Significantly greater than all other treatment groups,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

10 The results of this study indicated that as previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility in male rats in the FST compared to vehicle-treated animals. The  
15 magnitude of these changes are similar to those reported of our past studies with 10 mg/kg p.o. of fluoxetine. In contrast, climbing behavior was significantly decreased by a single p.o. administration of 10 mg/kg of fluoxetine compared to all other treatment groups. However, this  
20 could be related to the fact that fluoxetine has a much greater effect on swimming than climbing and it is likely that fluoxetine is not producing climbing as opposed to actually decreasing climbing. Finally, fluoxetine, as previously reported, does not significantly alter diving  
25 compared to vehicle-treated behavior.

A single p.o. administration of either 3 or 10 mg/kg of Example 49 did not significantly alter swimming, climbing, immobility or diving in male rats in the FST, indicating that at these doses using the p.o. route, Example 49 does not exhibit antidepressant action in the  
30 FST. In contrast, a single p.o. administration of 30

mg/kg of Example 49 produced a significant increase in swimming and a significant decrease in immobility compared to animals treated with vehicle, or 3 and 10 mg/kg of Example 49. However, the 30 mg/kg p.o. dose of Example 49 did not significantly alter diving or climbing counts compared to vehicle-treated animals. The increase in swimming counts produced by 30 mg/kg p.o. of Example 49 was comparable to that of 10 mg/kg of fluoxetine, although Example 49 was less effective than fluoxetine in reducing immobility.

In conclusion, a single p.o. administration of 30 mg/kg of Example 49 (one hour before the last swim test) increases swimming and decreases immobility counts in the FST, suggesting that Example 49 may have antidepressant properties in this model.

**H. Effect of a single p.o. administration of Example 22, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test**

Immobility

Statistical analysis indicated a significant effect of treatment on immobility (ANOVA,  $F(4,44) = 20.2$ ,  $p < 0.0001$ ). Post hoc analyses revealed that a single p.o. administration of 10 mg/kg of fluoxetine significantly decreased immobility (Student-Newman-Keuls value of 20.1) compared to vehicle-treated animals (Table 5g).

A single p.o. administration of 10 or 30 mg/kg doses of Example 22 produced a significant decrease in immobility compared to vehicle-treated animals (Student-Newman-Keuls

values of 12.2 and 55.0, respectively). In addition, the decrease in immobility produced by either fluoxetine or the 10 and 30 mg/kg doses of Example 22 (Student-Newman-Keuls values of 21.2, 13.0 and 56.8, respectively) was significantly greater than that of the 3 mg/kg dose of Example 22. The decrease in immobility produced by 30 mg/kg i.p. of Example 22 was significantly greater than that of the 10 mg/kg dose (Student-Newman-Keuls value 16.2). In addition, the magnitude of the decrease in immobility produced by 30 mg/kg of Example 22 was significantly greater than that of fluoxetine (Student-Newman-Keuls value of 9.3).

#### Swimming

Statistical analysis indicated a significant treatment effect on swimming behavior (ANOVA,  $F(4,44) = 35.00$ ,  $p < 0.0001$ ). Post hoc analyses revealed that a single i.p. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming compared to animals treated with vehicle, 3 or 10 mg/kg of Example 22 (Student-Newman-Keuls values of 49.6, 51.3 and 5.8, respectively) (Table 5g).

A single p.o. administration of 3 mg/kg did not significantly alter swimming behavior compared to vehicle-treated animals (Table 5g). However, a single p.o. administration of 30 mg/kg of Example 22 produced a significantly greater increase in swimming behavior compared to animals treated with vehicle, 3 or 10 mg/kg of Example 22 and fluoxetine (Student-Newman-Keuls values of 85.9, 88.1, 22.7 and 5.84, respectively).

Climbing behavior

There was a significant treatment effect on climbing behavior (ANOVA,  $F(4,44) = 4.1$ ,  $p = 0.0066$ ). Post hoc tests indicated that a single p.o. administration of 30  
5 mg/kg dose of Example 22 produced a significant increase in climbing compared to animals treated with vehicle, 3 or 10 mg/kg of Example 22 and fluoxetine (Student-Newman-Keuls values of 10.5, 11.1, 5.8 and 11.8, respectively).

10 Diving

Statistical analysis revealed that diving was not significantly altered by a single i.p. administration of 3, 10 or 30 mg/kg of Example 22 or 10 mg/kg of fluoxetine compared to vehicle-treated animals (ANOVA,  $F(4,44) =$   
15 0.58,  $p = 0.68$ ) (Table 5g).

TABLE 5g. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and Example 22 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

5

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	50 ± 1.6	2.1 ± 0.7	7.8 ± 1.0	0.3 ± 0.3
3 mg/kg EX22	50 ± 0.9	2.0 ± 0.6	7.6 ± 0.5	0.4 ± 0.4
10 mg/kg EX22	41 ± 1.3 <sup>c</sup>	2.9 ± 0.5	15.3 ± 0.8 <sup>g</sup>	0.4 ± 0.3
30 mg/kg EX22	31 ± 2.8 <sup>b</sup>	5.2 ± 1.0 <sup>a</sup>	23.2 ± 2.0 <sup>f</sup>	0.0 ± 0.0
10 mg/kg Fluox	39 ± 1.7 <sup>d</sup>	1.9 ± 0.5	19.2 ± 1.2 <sup>e</sup>	0.0 ± 0.0

Each value represents the mean ± S.E.M. A total of 10 animals were examined for each treatment group, except  
 10 for the 30 mg/kg dose of Example 22, where a total of 9 animals were examined.

Fluox = Fluoxetine, EX22 = Example 22. Experiments were conducted 1 hr. after the appropriate treatment.

15

<sup>a</sup>Significantly greater than the vehicle ( $p < 0.01$ ), 3 mg/kg Example 22 ( $p < 0.01$ ), 10 mg/kg Example 22 ( $p < 0.05$ ) and 10 mg/kg of fluoxetine ( $p < 0.05$ ), ANOVA and Student-Newman-Keuls test.

20



<sup>b</sup>Significantly less than all other treatment groups,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>c</sup>Significantly less than vehicle, 3 and 30 mg/kg of Example 22 ( $p < 0.01$ ) and 10 mg/kg of fluoxetine ( $p < 0.05$ ), ANOVA and Student-Newman-Keuls.

<sup>d</sup>Significantly less than vehicle, 3 and 30 mg/kg of Example 22,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>e</sup>Significantly greater than the vehicle, 3 and 10 mg/kg of Example 22,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>f</sup>Significantly greater than the vehicle, 3 and 10 mg/kg of Example 22,  $p < 0.01$  and fluoxetine,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>g</sup>Significantly greater than the vehicle and 3 mg/kg of Example 22,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

The results of this study indicated that as previously reported, a single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming and a significant decrease in immobility in male Sprague-Dawley rats in the FST compared to vehicle-treated animals. The magnitude of these changes are similar to those reported of our past studies with 10 mg/kg p.o. of fluoxetine. In contrast, neither climbing nor diving

behavior was significantly altered by a single i.p. administration of 10 mg/kg of fluoxetine.

A single p.o. administration of 3 mg/kg of Example 22 did not significantly alter swimming in male rats in the FST. In contrast, a single p.o. administration of 10 or 30 mg/kg of Example 22 produced a significant increase in swimming and a significant decrease in immobility compared to animals treated with vehicle or 3 mg/kg of Example 22. In addition, the magnitude of the increase in swimming behavior produced by 30 mg/kg p.o. of Example 22 was significantly greater than that of 10 mg/kg of Example 22 and 10 mg/kg of fluoxetine. The rank order of the treatments for increasing swimming is: 30 mg/kg Example 22 > fluoxetine > 10 mg/kg Example 22 > 3 mg/kg Example 22

Climbing behavior was significantly greater in animals treated with 30 mg/kg p.o. of Example 22 compared to animals treated p.o. with either vehicle, 3 or 10 mg/kg of Example 22 or 10 mg/kg of fluoxetine. None of the other treatments besides 30 mg/kg of Example 22 significantly altered climbing behavior compared to vehicle-treated animals. The rank order of the treatments for increasing climbing is: 30 mg/kg Example 22 >> 3 Mg/kg Example 22 = 10 mg/kg Example 22 = fluoxetine.

A single p.o. administration of 3 mg/kg of Example 22 did not significantly alter swimming compared to vehicle-treated animals. However, the 10 and 30 mg/kg doses produced a significantly greater decrease in immobility

compared to vehicle-treated animals, with the effect at 30 mg/kg being greater than that of 10 mg/kg. Furthermore, 30 mg/kg p.o. of Example 22 produced a significantly greater decrease in immobility than 10 mg/kg p.o. of fluoxetine. The rank order of the treatments for decreasing immobility is 30 mg/kg Example 22 > 10 mg/kg Example 22 = fluoxetine > 3 mg/kg Example 22.

In conclusion, a single p.o. administration of 10 or 30 mg/kg of Example 22 significantly increases swimming and significantly decreases immobility in vehicle-treated male Sprague-Dawley rats. This suggests that at these doses, Example 22 has antidepressant properties.

15

I. Effect of a single p.o. administration of Example 95, fluoxetine and vehicle on swimming, climbing, immobility and diving in the forced swim test

Statistical analysis indicated that a single p.o. administration of 10 or 30 mg/kg Example 95 significantly increased rat immobility and significantly decreased swim behavior in the rat forced swim test at both doses (Table 5h,  $p < 0.01$ , ANOVA and Student-Newman-Keuls, respectively).

TABLE 5h. The effect of a single p.o. administration of vehicle, 10 mg/kg of fluoxetine and 3, 10 or 30 mg/kg of Example 95 on immobility, climbing, diving and swimming in the forced swim test in male Sprague-Dawley rats.

5

Treatment	Immobility	Climbing	Swimming	Diving
Vehicle	42 ± 1.7	2.3 ± 0.5	14.7 ± 1.0	0.1 ± 0.1
3 mg/kg EX95	40 ± 3.3	2.6 ± 0.8	17.1 ± 2.5	0.0 ± 0.0
10 mg/kg EX95	52 ± 1.2 <sup>a</sup>	1.3 ± 0.5	6.9 ± 0.9 <sup>b</sup>	0.1 ± 0.1
30mg/kg EX95	54 ± 0.9 <sup>a</sup>	1.0 ± 0.3	4.8 ± 0.7 <sup>b</sup>	0.0 ± 0.0
10 mg/kg Fluox	38 ± 2.2	1.9 ± 0.6	20.0 ± 1.5 <sup>c</sup>	0.1 ± 0.1

Each value represents the mean ± S.E.M. A total of 8 animals were examined for each treatment group, except for the vehicle, where a total of 10 animals were examined. Fluox = Fluoxetine; EX95 = Example 95. Experiments were conducted 1 hr. after the appropriate treatment.

<sup>a</sup>Significantly less than Vehicle, 3 mg/kg of Example 95 and 10 mg/kg of fluoxetine,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>b</sup>Significantly less than Vehicle, 3 mg/kg of Example 95 and 10 mg/kg of fluoxetine,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

<sup>c</sup>Significantly greater than Vehicle ( $p < 0.05$ ), 10 and 30 mg/kg of Example 95 ( $p < 0.01$ ), ANOVA and Student-Newman-Keuls test.

5

A single p.o. administration of 10 mg/kg of fluoxetine produced a significant increase in swimming behavior compared to vehicle-treated animals. In addition, fluoxetine significantly decreased immobility compared to vehicle-treated animals. A single p.o. administration of 3 mg/kg of Example 95 did not significantly alter swimming, climbing, immobility or diving behavior compared to vehicle-treated animals. In contrast, a single p.o. administration of either 10 or 30 mg/kg of Example 95 produced a significant increase in immobility and a significant decrease in swimming behavior compared to vehicle-treated animals. There was no significant difference in the magnitude of change in swimming and immobility between the 10 and 30 mg/kg doses of Example 95.

These data indicate that at a doses of 10 and 30 mg/kg p.o., Example 95 produced effects opposite of that seen with antidepressants in the rat forced swim test, suggesting that Example 95 does not produce antidepressant-like actions in the forced swim test in male Sprague-Dawley rats.

30

## 2. Social Interaction Test

### A. The Effect Of Example 92 And Chlordiazepoxide On Behavior In Th Rat Social Interaction Test

5 A single i.p. administration of either 10 or 30 mg/kg of Example 92 significantly increased social interaction (Table 6 and Figure 4), as did the benzodiazepine anxiolytic, chlordiazepoxide (Student-Newman-Keuls value of 31.3) compared to vehicle-treated animals [ANOVA, 10  $F(4,45) = 10.3$ ,  $p < 0.0001$ ; Student-Newman-Keuls values for the 10 and 30 mg/kg doses were 8.61 and 19.55, respectively]. However, the 100 mg/kg i.p. dose of Example 92 did not significantly alter social interaction time compared to vehicle-treated animals (Table 6 and 15 Figure 4). The degree of social interaction was greater in the chlordiazepoxide-treated animals compared to those that received either the 10 or 30 mg/kg doses of Example 92.

**Table 6. The Effect Of A Single Injection Of Vehicle, Chlordiazepoxide And Example 92 On The Social Interaction And Rearing Of Unfamiliar Cage Mates In A Familiar Arena**

5

Drug Social Treatment (i.p.) Interaction (sec)<sup>a</sup>

Vehicle, 1 ml/kg	96 ± 12
Chlordiazepoxide, 5 mg/kg	188 ± 15 <sup>b</sup>
Example 92, 10 mg/kg	144 ± 12 <sup>b</sup>
Example 92, 30 mg/kg	169 ± 13 <sup>c</sup>
Example 92, 100 mg/kg	117 ± 6 <sup>d</sup>

<sup>a</sup> Each value represents the mean seconds of social interaction ± S.E.M.

10

<sup>b</sup> Significantly greater than Vehicle,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>c</sup> Significantly greater than Vehicle,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

15

<sup>d</sup> Significantly less than 30 mg/kg dose and chlordiazepoxide,  $p < 0.01$ , ANOVA and Student-Newman-Keuls.

20

B. The Effect Of Example 92 And Chlordiazepoxide On Rearing Behavior, Locomotor Activity And Grooming In The Rat Social Interaction Test

5 The administration of 10 and 30 mg/kg, but not 100 mg/kg of Example 92, significantly increased rearing behavior compared to either vehicle or chlordiazepoxide [ANOVA,  $F(4,45) = 2.6$ ,  $p = 0.046$ ; See Table 13]. In addition, the number of rearings at the 10 mg/kg dose of Example 92  
10 was significantly greater than that produced by chlordiazepoxide (Table 13).

The administration of either Example 92 or chlordiazepoxide did not significantly alter the number  
15 of grooming bouts compared to vehicle-treated animals [ $F(4,45) = .67$ ,  $p = 0.62$ ].

A single injection of either 10 or 30 mg/kg i.p. of Example 92 or 5 mg/kg i.p. of chlordiazepoxide did not  
20 significantly alter the number of squares crossed (Table 13). However, the number of squares crossed following the 100 mg/kg dose of Example 92 was significantly lower than animals treated with either vehicle, 10 mg/kg i.p. of Example 92, 30 mg/kg i.p. of Example 92 or 5 mg/kg  
25 i.p. of chlordiazepoxide. [ANOVA,  $F(4,43) = 6.94$ ,  $p = 0.0002$ ].



**Table 13. The Effect of a Single Injection of Vehicle, Chlordiazepoxide and Example 92 on the Number of Rearings, Squares Crossed and Grooming Bouts in the Rat Social Interaction Test.**

Drug Treatment (i.p.)	Rearings	Squares Crossed	Grooming Bouts
Vehicle, 1 ml/kg	33 ± 4	393 ± 26	5.1 ± 1.1
Chlordiazepoxide, 5 mg/kg	30 ± 2	287 ± 28	7.3 ± 1.3
Example 92, 10 mg/kg	47 ± 8 <sup>a</sup>	298 ± 40	6.1 ± 0.5
Example 92, 30 mg/kg	45 ± 5 <sup>b</sup>	368 ± 36	6.2 ± 0.7
Example 92, 100 mg/kg	31 ± 4	195 ± 19 <sup>c</sup>	6.8 ± 1.3

All values represent the mean ± S.E.M.

<sup>a</sup> Significantly greater than chlordiazepoxide,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test

<sup>b</sup> Significantly greater than vehicle and chlordiazepoxide,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>c</sup> Significantly less than 10 & 30 mg/kg of Example 92 ( $p < 0.01$ ), vehicle ( $p < 0.01$ ) and chlordiazepoxide ( $p < 0.05$ ), ANOVA and Student-Newman-Keuls test.

At doses of 10 and 30 mg/kg i.p., Example 92 produced a significant increase in social interaction time in male rats compared to vehicle-treated animals. Also, the anxiolytic agent (5 mg/kg i.p. chlordiazepoxide) produced a significant increase in social interaction time compared to vehicle-treated animals. The response produced by the 30 mg/kg dose of Example 92 was comparable to that of the positive control, chlordiazepoxide. The 30 mg/kg dose of Example 92 produced a significant increase in rearing compared to vehicle- and chlordiazepoxide-treated animals. Previously, it has been shown that in the Social Interaction Test, psychostimulants such as amphetamine and caffeine, increase social interaction and locomotor activity, whereas anxiolytics increase social interaction time. (File, 1985; File and Hyde, 1979; Guy and Gardner, 1985). Consistent with an increase in social interaction, Example 92 increased rearing behavior. However, it did not produce an increase in horizontal locomotor activity or grooming bouts. In addition, Example 92 did not elicit stereotypes or produce aggressive behaviors. In fact, locomotor activity as measured by squares crossed was significantly reduced at the 100 mg/kg i.p. dose of Example 92 compared to vehicle-treated animals. This decrease in locomotor activity did not appear to be accompanied by ataxia or sedation. Thus, it is unlikely that Example 92 is producing a non-specific effect on social interaction through motor stimulation. In order to justify this claim, in another study (not reported), the effect of Example 92 was dosed to familiar cage mates in the social interaction test and no significant increase in interaction in this variation of the Social Interaction Test was observed. In this test, the anxiogenic stimulus

of a novel partner is removed and therefore only locomotor activity and normal behavior are observed (Guy and Gardner, 1985). In conclusion, the results of this study indicate that Example 92, at doses of 10 and 30 mg/kg i.p., significantly increases social interaction time without producing an increase in horizontal locomotor activity or grooming bouts. Furthermore, the effect produced by the 30 mg/kg of Example 92 was comparable to that observed for 5 mg/kg of chlordiazepoxide, the active control. No increase in social interaction was observed at the 100 mg/kg dose of Example 92. However, a decrease in the number of squares crossed was observed. In summary, Example 92 has the profile of an anxiolytic drug in the Social Interaction Test.

15

C. The effect of a single p.o. administration of Example 34, vehicle and chlordiazepoxide on the duration of social interaction in the rat social interaction test.

20 There was a significant treatment effect on the duration of social interaction (ANOVA,  $F(5,40) = 11.8$ ,  $p < 0.001$ ). Subsequent post hoc analyses indicated that a single p.o. administration of either 0.03, 0.1, 0.3 and 1 mg/kg of Example 34 (Student-Newman-Keuls test values of 8.0, 25 10.6, 4.3 and 13.2, respectively) significantly increased social interaction, as did chlordiazepoxide (Student-Newman-Keuls value of 57.1), compare to vehicle-treated animals (Table 6a). The duration of social interaction produced by chlordiazepoxide was significantly greater 30 than that of 0.03, 0.1, 0.3 and 1 mg/kg p.o. of Example 34 (Student-Newman-Keuls values of 19.6, 18.6, 26.2 and 17.6, respectively). There was no significant difference

in the duration of social interaction between the various doses of Example 34 (Table 6a).

5 **Table 6a. The effect of a single p.o. administration of vehicle, chlordiazepoxide and Example 34 on social interaction time in unfamiliar cage mates in a familiar arena**

10 Drug Treatment (p.o.)	Social Interaction (sec)
Vehicle, 1 ml/kg	27 ± 1.4 <sup>A</sup>
Chlordiazepoxide, 5 mg/kg	122 ± 18 <sup>S</sup>
Example 34, 0.03 mg/kg	62 ± 11 <sup>*</sup>
Example 34, 0.1 mg/kg	66 ± 7 <sup>*</sup>
Example 34, 0.3 mg/kg	53 ± 6 <sup>*</sup>
Example 34, 1 mg/kg	69 ± 6 <sup>#</sup>

Animals received one p.o administration of the appropriate treatment and all experiments were conducted one hour after the last injection.

15

<sup>A</sup>Each value represents the mean seconds of social interaction ± S.E.M. A total of 6-8 animals were examined for each treatment group.

20 <sup>\*</sup>Significantly greater than Vehicle,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>#</sup>Significantly greater than Vehicle,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

25 <sup>S</sup>Significantly greater than all other treatment groups,  $p < 0.01$ , ANOVA and Student-Newman-Keuls test.

D. The effect of a single p.o. administration of Example 34, vehicle and chlordiazepoxide on rearing behavior, locomotor activity and grooming in the social interaction test.

5

Statistical analysis indicated a significant effect of treatment on rearing behavior (ANOVA,  $F(5,40) = 3.5$ ,  $p = 0.01$ ; Table 14). Post hoc analyses revealed that the the number of rears following 0.3 mg/kg of Example 34 was significantly lower than that of 0.1 and 1 mg/kg p.o. of Example 34 (Student-Newman-Keuls values of 8.8 and 9.4, respectively).

15

Statistical analysis indicated a significant effect of treatment on number of squares crossed ( $F(5,40) = 2.9$ ,  $p = 0.03$ ). Post hoc analyses indicated that a single p.o. administration of 0.3 mg/kg of Example 34 produced a significantly greater effect on the number of squares crossed compared to vehicle-treated animals (Student-Newman-Keuls values of 10.4).

20

Statistical analysis indicated a significant effect of treatment on grooming behavior ( $F(5,40) = 4.3$ ,  $p = 0.004$ ). Post hoc analyses indicated that the number of grooming episodes was significantly lower in the 0.03 mg/kg group compared to animals treated with 0.1, 0.3 or 1 mg/kg p.o. of Example 34 (Student-Newman-Keuls values of 11, 8 and 9.7, respectively (Table 14). In addition, the number of grooming episodes was significantly greater in animals treated with 0.1 mg/kg p.o. of Example 34 compared to those treated with vehicle (Table 14).

30

Table 14. The effect of a single p.o. administration of vehicle, chlordiazepoxide and Example 34 on the number of rearings, grooming episodes and squares crossed in the social interaction test in unfamiliar cage mates in a familiar arena

Drug Treatment (p.o.)	Rearing	Squares Crossed	Grooming bouts
Vehicle, 1 ml/kg	$34 \pm 3$	$250 \pm 31$	$4.6 \pm 0.7$
Chlordiazepoxide, 5 mg/kg	$35 \pm 2$	$265 \pm 30$	$5.3 \pm 0.7$
Example 34, 0.03 mg/kg	$27 \pm 3^*$	$312 \pm 23$	$4.0 \pm 0.4^{\&}$
Example 34, 0.1 mg/kg	$40 \pm 5$	$295 \pm 40$	$7.6 \pm 0.5^*$
Example 34, 0.3 mg/kg	$27 \pm 2^{\&}$	$363 \pm 17$	$7.2 \pm 1.1$
Example 34, 1 mg/kg	$40 \pm 1$	$343 \pm 15^{\&}$	$7.3 \pm 0.8$

10 Animals received one p.o administration of the appropriate treatment and all experiments were conducted one hour after the last injection. All values represent the mean  $\pm$  S.E.M. A total of 6-8 animals were examined for each treatment group.

15

\*Significantly less than 0.1 mg/kg of Example 34,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test. .

$\&$ Significantly less than 0.1 and 1mg/kg of Example 34,  $p < 20$  0.05, ANOVA and Student-Newman-Keuls test.

<sup>@</sup>Significantly greater than Vehicle,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>^</sup>Significantly less than 0.1, 0.3 and 1 mg/kg of Example 34,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

<sup>\*</sup>Significantly greater than Vehicle,  $p < 0.05$ , ANOVA and Student-Newman-Keuls test.

10 One of the main findings of this study was that in paired, unfamiliar male Sprague-Dawley rats, a single p.o. administration of either 0.03, 0.1, 0.3 or 1 mg/kg p.o. of Example 34 produced a significant increase (2-2.6 fold) in the duration of social interaction compared to  
15 animals treated with vehicle. In addition, there was no significant difference in the magnitude of increase in social interaction between the various doses of Example 34, i.e. there was no dose-response relationship. As previously reported, a single p.o. administration of 5  
20 mg/kg of chlordiazepoxide produced a significant increase in the duration of social interaction compared to vehicle-treated animals.

Rearing behavior was not significantly altered by any of  
25 the doses of Example 34 or by chlordiazepoxide compared to vehicle-treated animals, although there were differences between the doses of Example 34. The number of squares crossed was significantly greater following a single p.o. administration of 1 mg/kg of Example 34  
30 compared to vehicle-treated animals, whereas there were no significant differences between the other doses of Example 34 and vehicle. Thus, overall, Example 34 does

not significantly alter locomotor activity, suggesting that it does not produce locomotor activation or stimulation.

- 5 Grooming behavior following a single p.o. administration tended to be greater after 0.1, 0.3 and 1 mg/kg of Example 34 compared to animals that had received vehicle, although this was only statistically significant for the 0.1 mg/kg dose. Furthermore, the number of grooming  
10 episodes was significantly lower after a single p.o. administration of 0.03 mg/kg of Example 34 compared to 0.1, 0.3 and 1 mg/kg of Example 34.

In conclusion, the above results suggest that a single  
15 p.o. administration of 0.03, 0.1, 0.3 or 1 mg/kg of Example 34 produces an anxiolytic action in the social interaction test in male Sprague-Dawley rats.



### III Binding Properties of Compounds at Cloned Receptors

#### A. Materials and Methods

The binding properties of the compounds of the present invention were evaluated at one or more cloned receptors or native, tissue-derived transporters, using protocols described below.

#### Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin) at 37°C with 5% CO<sub>2</sub>. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin) at 37°C with 5% CO<sub>2</sub>. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LM(tk-) cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin, 100 µg/mL streptomycin) at 37°C with 5% CO<sub>2</sub>. Stock plates of LM(tk-) cells were trypsinized and split 1:10 every 3-4 days. Chinese Hamster Ovary (CHO) cells were grown on 150 mm plates in HAM's F12 medium with (HAM's F-12 with 10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin, 100 µg/mL streptomycin) at 37°C with 5% CO<sub>2</sub>. Stock plates of CHO cells were trypsinized and split 1:8 every 3-4 days.

LM(tk-) cells were stably transfected with the human GAL1 or GAL3 receptor. CHO cells were stably transfected with the human GAL2 receptor.

#### 5 Stable Transfection

cDNAs for the human and rat GAL1, and human and rat GAL3 receptors were transfected with a G-418 resistant gene into the mouse fibroblast LM(tk-) cell line by a calcium phosphate transfection method (Cullen, 1987). Stably  
10 transfected cells were selected with G-418. Human and rat GAL2 receptors were similarly transfected into CHO cells.

#### Membrane Harvest

Membranes were harvested from stably transfected LM(tk-) cells. Adherent cells were washed twice in ice-cold  
15 phosphate buffered saline (138 mM NaCl, 8.1 mM Na<sub>2</sub>HPO<sub>4</sub>, 2.5 mM KCl, 1.2 mM KH<sub>2</sub>PO<sub>4</sub>, 0.9 mM CaCl<sub>2</sub>, 0.5 mM MgCl<sub>2</sub>, pH 7.4) and lysed by sonication in ice-cold sonication buffer (20 mM Tris-HCl, 5 mM EDTA, pH 7.7). Large  
20 particles and debris were cleared by low speed centrifugation (200 x g, 5 min, 4°C). Membranes were collected from the supernatant fraction by centrifugation (32,000 x g, 18 min, 4°C), washed with ice-cold hypotonic buffer, and collected again by centrifugation (32,000 x  
25 g, 18 min, 4°C). The final membrane pellet was resuspended by sonication into a small volume of ice-cold binding buffer (~1 ml for every 5 plates: 10 mM NaCl, 20 mM HEPES, 0.22 mM KH<sub>2</sub>PO<sub>4</sub>, 1.26 mM CaCl<sub>2</sub>, 0.81 mM MgSO<sub>4</sub>, pH 7.4). Protein concentration was measured by the Bradford  
30 method (Bradford, 1976) using Bio-Rad Reagent, with bovine serum albumin as a standard. Membranes were held on ice for up to one hour and used fresh, or flash frozen

and stored in liquid nitrogen. Membranes were prepared similarly from CHO cells.

As described in the Background of the Invention,  
5 compounds that block the effects of galanin on the GAL3  
receptor subtype can potentially be used for the  
treatment of depression and anxiety. Biogenic amine  
transmitter molecules that mediate neuronal signals are  
currently known in the art and include among others  
10 serotonin (5HT), norepinephrine (NE), and dopamine (DA).  
Recent advances in the molecular studies of the  
mechanisms for these transmitter molecules, together with  
the characterization of their pharmacological properties,  
has enabled the identification of numerous potential  
15 targets for therapeutic intervention. Inhibitors of the  
5HT, NE and DA transporter systems, and inhibitors of the  
enzyme, monoamine oxidase, have been widely studied and  
are known to enhance the action of biogenic amine  
neurotransmitters. The resultant clinically effective  
20 antidepressant drugs are known today as TCAs, SSRIs and  
MAOIs. (Tatsumi et al., 1997; Iversen, 2000).

In the case of galanin, the evidence presented in this  
invention suggests that GPCR-targeted molecules that bind  
25 to and antagonize the GAL3 receptor may be used for the  
treatment of depression and/or anxiety disorders. Another  
approach could involve the administration of an  
antagonist of the GAL3 receptor, such as those described  
herein, which also possesses 5HT<sub>4</sub> receptor antagonist  
30 properties (Kennett et al., 1997). A further approach  
could involve the administration of a GAL3 antagonist,  
such as those described herein, which also possesses 5HT<sub>1A</sub>

- receptor binding properties (Razani et al., 1997). However, in any case the GAL3 antagonist(s) should be free of activity at the human GAL1 receptor and the 5HT, NE and DA transporters. Furthermore, the GAL3 antagonist(s) should not inhibit the enzymatic activity of monoamine oxidase A (MAO<sub>A</sub>) or monoamine oxidase B (MAO<sub>B</sub>) present in the brain (i.e. central MAO). The design of such compounds can be optimized by determining their binding affinity at the recombinant GAL3, GAL1, 5HT<sub>4</sub>, and 5HT<sub>1A</sub> receptors; and the native 5HT, NE and DA transporters. The design of such compounds can be further optimized by determining their interaction with central MAO<sub>A</sub> and central MAO<sub>B</sub>.
- Additionally, the GAL3 antagonist(s) would optimally not bind at the following receptors due to possible side effects: human GAL2; human H<sub>1</sub> histamine; human  $\alpha_{1A}$  adrenergic, human  $\alpha_{1B}$  adrenergic, human  $\alpha_{1D}$  adrenergic, human  $\alpha_{2A}$  adrenergic, human  $\alpha_{2B}$  adrenergic, and human  $\alpha_{2C}$  adrenergic; human dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>; and the human 5HT<sub>1B</sub>, human 5HT<sub>1D</sub>, human 5HT<sub>1E</sub>, human 5HT<sub>1F</sub>, human 5HT<sub>2A</sub>, rat 5HT<sub>2C</sub>, human 5HT<sub>6</sub>, and human 5HT<sub>7</sub> receptors.

#### Radioligand Binding Assays and Enzymatic Assays

- The methods to obtain the cDNA of the receptors, express said receptors in heterologous systems, and carry out assays to determine binding affinity are described as follows.
- Galanin Receptors: Binding assays were performed according to the following published methods: human GAL3 (PCT International Publication No. WO 98/15570), human

GAL1 (PCT International Publication No. WO 95/2260),  
human GAL2 (PCT International Publication No. WO  
97/26853).

5 Human 5HT<sub>1B</sub>, 5HT<sub>1D</sub>, 5HT<sub>1E</sub>, 5HT<sub>1F</sub>, and 5HT<sub>7</sub> Receptors: The  
cell lysates of LM(tk-) clonal cell line stably  
transfected with the genes encoding each of these 5HT  
receptor-subtypes were prepared as described above. Cell  
membranes were suspended in 50mM Tris-HCl buffer (pH 7.4  
10 at 37°C) containing 10 mM MgCl<sub>2</sub>, 0.2 mM EDTA, 10 M  
pargyline, and 0.1% ascorbate. The affinities of  
compounds were determined in equilibrium competition  
binding assays by incubation for 30 minutes at 37 °C in  
the presence of 5 nM [<sup>3</sup>H]-serotonin. Nonspecific binding  
15 was determined in the presence of 10 µM serotonin. The  
bound radioligand was separated by filtration through  
GF/B filters using a cell harvester.

Human 5HT<sub>2A</sub> Receptor: The coding sequence of the human  
20 5HT<sub>2A</sub> receptor was obtained from a human brain cortex cDNA  
library, and cloned into the cloning site of pCEXV-3  
eukaryotic expression vector. This construct was  
transfected into COS-7 cells by the DEAE-dextran method  
(Cullen, 1987). Cells were harvested after 72 hours and  
25 lysed by sonication in 5 mM Tris-HCl, 5 mM EDTA, pH 7.5.  
The cell lysates were subjected to centrifugation at 1000  
rpm for 5 minutes at 4°C, and the supernatant was  
subjected to centrifugation at 30,000 x g for 20 minutes  
at 4°C. The pellet was suspended in 50 mM Tris-HCl buffer  
30 (pH 7.7 at room temperature) containing 10 mM MgSO<sub>4</sub>, 0.5  
mM EDTA, and 0.1% ascorbate. The affinity of compounds at  
5HT<sub>2A</sub> receptors were determined in equilibrium competition

binding assays using [<sup>3</sup>H]ketanserin (1 nM). Nonspecific binding was defined by the addition of 10 μM mianserin. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

5

5-HT<sub>1A</sub> Receptor: The cDNA corresponding to the 5-HT<sub>1A</sub> receptor open reading frames and variable non-coding 5'- and 3'-regions, was cloned into the eukaryotic expression vector pCEXV-3. These constructs were transfected transiently into COS-7 cells by the DEAE-dextran method (Cullen, 1987), and harvested after 72 hours. Radioligand binding assays were performed as described above for the 5-HT<sub>2A</sub> receptor, except that <sup>3</sup>H-8-OH-DPAT was used as the radioligand and nonspecific binding was determined by the addition of 10 μM mianserin.

10  
15

Other 5-HT Receptors: Other serotonin receptor binding assays were performed according to published methods: rat 5HT<sub>2c</sub> receptor (Julius et al., 1988); and 5-HT<sub>6</sub> (Monsma, et al., 1993). The binding assays using the 5-HT<sub>4</sub> receptor were performed according to the procedures described in U.S. Patent No. 5,766,879, the disclosure of which is hereby incorporated by reference in its entirety into this application.

Other receptors: Cell membranes expressing human dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>4</sub> and rat D<sub>3</sub> receptors were purchased through BioSignal, Inc. (Montreal, Canada). Binding assays using the histamine H<sub>1</sub> receptor; dopamine receptors; and  $\alpha_{1A}$ ,  $\alpha_{1B}$ , and  $\alpha_2$  adrenergic receptors may be carried out according to the procedures described in U.S. Patent No. 5,780,485, the disclosure of which is hereby incorporated by reference in its entirety into this application. Binding assays using the dopamine D<sub>5</sub> receptor may be carried out according to the procedures described in U.S. Patent No. 5,882,855, the disclosure of which is hereby incorporated by reference in its entirety into this application. Binding assays for the human  $\alpha_{1D}$  adrenergic receptor may be carried out according to the procedures described in U.S. Patent No. 6,156,518, the disclosure of which is hereby incorporated by reference in its entirety into this application.

The methods to determine binding affinity at native transporters are described in the following publications: 5HT transporter and NE transporter (Owens

et al., 1997), and DA transporter (Javitch et al, 1984).

5 The methods to determine activity at monoamine oxidase enzymes (for example, central MAO<sub>A</sub> and MAO<sub>B</sub>) are described by Otsuka and Kobayashi, 1964, and were performed by NovaScreen (Hanover, MD) with the following modifications.

10 Central Monoamine Oxidase A Enzyme Assay: Rat brain was used as the enzyme source. The enzyme source was pre-incubated with reference compound (RO 41-1049), test compound (Example 92), and subtype selective blocker (100nM deprenyl) for 60 minutes at 37°C in 50 mM  
15 KPO<sub>4</sub> containing 50 µM EDTA and 10 µM dithiothreitol (pH 7.2 at 25°C). Substrate ([<sup>14</sup>C]Serotonin, 45-60 Ci/mmol) was then added and incubated for 30 minutes. The reaction was stopped by the addition of 0.5 ml of 1-2M citric acid. Radioactive product was extracted into  
20 xylene/ethyl acetate fluor and compared to control values by scintillation spectrophotometry in order to ascertain any interactions of test compound with central MAO<sub>A</sub>.

25 Central Monoamine Oxidase B Enzyme Assay: Rat brain was used as the enzyme source. The assay was performed as described above for central MAO<sub>A</sub>, except the reference compound was RO 166491 and the subtype selective blocker was 100 nM clorgyline. Also, the  
30 substrate ([<sup>14</sup>C]Phenylethylamine, 0.056 Ci/mmol) was added and incubated for 10 minutes.



### Materials

Cell culture media and supplements were from Specialty Media (Lavallette, NJ). Cell culture plates (150 mm and 96-well microtiter) were from Corning (Corning, NY).  
5 Polypropylene 96-well microtiter plates were from Costar (Cambridge, MA). Bovine serum albumin (ultra-fat free, A-7511) was from Sigma (St. Louis, MO). All radioligands were from New England Nuclear (Boston, MA). Commercially available peptides and peptide  
10 analogs were either from Bachem California (Torrance, CA) or Peninsula (Belmont, CA). All other materials were reagent grade.

### Data Analysis

15 Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA). Enzymatic assay data were derived from a standard curve of reference compound data.

20

The selectivity ratios for compounds of the claimed invention were calculated from the binding data presented in Tables 1-4, Table 7 and Table 9 of the subject application. More specifically, these ratios  
25 were calculated by dividing (a) the binding affinity ( $K_i$  value) of said compound to a particular receptor or transporter by (b) the binding affinity ( $K_i$  value) of said compound to the human GAL3 receptor. The data presented in Table 8 and Table 10, hereinafter, were  
30 calculated using the above described method.

For example, the GAL3/GAL1 selectivity ratio of 10-fold recited in claim 110 of the subject application is characteristic of Example 34. This binding ratio was calculated by dividing (a) the  $K_i$  value of 912 for the binding of Example 34 to the GAL1 receptor (see Table 1) by (b) the  $K_i$  value of 23 for the binding of Example 34 to the human GAL3 receptor, thus obtaining the result of 39. Therefore the GAL3/GAL1 binding ratio for Example 34 was determined to be greater than 10-fold.

#### B. Results

The compounds described in the claimed invention were assayed using a panel of cloned receptors and native transporters. The preferred compounds were found to be selective GAL3 antagonists. The binding affinities and selectivity ratios of several compounds are illustrated in Tables 7-10.

Table 7: Antagonist binding affinity (Ki) at the human GAL3 receptor vs. serotonin receptors and several transporters.

Example	hGAL3	h5HT <sub>1A</sub>	h5HT <sub>1B</sub>	h5HT <sub>1D</sub>	h5HT <sub>1E</sub>	h5HT <sub>1F</sub>	h5HT <sub>2A</sub>	r5HT <sub>2C</sub>	h5HT <sub>4</sub>	h5HT <sub>6</sub>	h5HT <sub>7</sub>	r5HT <sub>7</sub>	rNE	rDA
	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Uptk (nM)	Uptk (nM)
11	91	4682	101	102	9174	1780	6708	802	1308	800	1012	1595	*	5430
15	73	5098	487	1272	11038	4192	11270	572	2301	1457	2527	1737	*	24500
17	87	3477	407	1032	33523	10271	7157	562	2606	711	1797	719	18325	27200
22	28	9714	1981	1852	13230	5773	20689	1717	2457	2264	2672	8483	13085	7480
34	23	*	1059	2976	28282	4803	*	2076	20762	38921	4439	37462	*	3900
49	211	29187	8447	16872	23886	8894	*	6687	13230	13	12268	40666	37585	2010
60	86	33666	5461	9198	1180	2124	26118	1781	1180	47536	3235	25274	46108	14500
77	79	5472	365	716	5888	3237	2242	456	1324	503	1547	821	28083	2790
92	38	*	11323	32139	18934	5290	*	ND	72	*	ND	45111	33879	17800
94	49	*	3349	10764	25227	5683	*	4099	4120	3647	8018	12961	4876	2200
95	29	28288	5226	16018	27211	4446	*	3471	3031	21507	11638	*	6101	12000
97	51	*	5057	14235	22692	4157	*	1950	2550	29131	11283	36308	4412	8440
98	38	24576	2419	9118	16240	3359	*	2260	1210	14018	8464	36329	5496	7430

\* = >50000  
ND = Not determined

Table 8: Antagonist selectivity ratios determined for the human GAL3 receptor vs. serotonin receptors and several transporters.

Example	hGAL3	h5HT <sub>1A</sub>	h5HT <sub>1B</sub>	h5HT <sub>1D</sub>	h5HT <sub>1E</sub>	h5HT <sub>1F</sub>	h5HT <sub>2A</sub>	r5HT <sub>2C</sub>	h5HT <sub>4</sub>	h5HT <sub>6</sub>	h5HT <sub>7</sub>	r5HT <sub>7</sub> Uptk	rNE Uptk	rDA Uptk
11	1	>30	1	1	>100	20	>30	9	14	9	11	18	>100	>30
15	1	>30	7	17	>100	>30	>100	8	>30	20	>30	24	>100	>100
17	1	>30	5	12	>100	>100	>30	6	30	8	21	8	>100	>100
22	1	>100	>30	>30	>100	>100	>100	>30	>30	>30	>30	>100	>100	>100
34	1	>100	>30	>100	>100	>100	>100	>30	>100	>100	>100	>100	>100	>100
49	1	>100	>30	>30	>100	>30	>100	>30	>30	0	>30	>100	>100	10
60	1	>100	>30	>100	14	25	>100	21	14	>100	>30	>100	>100	>100
77	1	>30	5	9	>30	>30	28	6	17	6	20	10	>100	>30
92	1	>100	>100	>100	>100	>100	>100	ND	2	>100	ND	>100	>100	>100
94	1	>100	>30	>100	>100	>100	>100	>30	>30	>30	>100	>100	>30	>130
95	1	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
97	1	>100	>30	>100	>100	>30	>100	>30	>30	>100	>100	>100	>30	>100
98	1	>100	>30	>100	>100	>30	>100	>30	>30	>100	>100	>100	>100	>100

ND = Not determined

Table 9: Antagonist binding affinity (Ki) at the human GAL3 receptor vs. alpha-adrenergic, dopamine, and histamine receptors.

Example	hGAL3	h $\alpha_{1A}$	h $\alpha_{1B}$	h $\alpha_{1D}$	h $\alpha_{2A}$	h $\alpha_{2B}$	h $\alpha_{2C}$	hD <sub>1</sub>	hD <sub>2</sub>	rD <sub>3</sub>	hD <sub>4</sub>	hD <sub>5</sub>	hH <sub>1</sub>
	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)
11	91	926	1436	264	1819	10235	3004	79	782	2139	4828	64	ND
15	73	3392	853	480	14413	24515	8202	344	2184	8809	13151	78	ND
17	87	996	1167	221	3523	38732	10269	516	1808	2477	22227	89	ND
22	28	1278	1582	368	906	5757	2737	128	1501	5664	11621	63	ND
34	23	3756	15004	1240	3679	15488	8832	290	2500	9922	18716	111	ND
49	211	6646	18852	678	4731	25374	9244	3781	5940	13964	45824	328	ND
60	86	13604	40615	4231	10838	*	7200	600	26815	15295	48756	538	39909
77	79	834	452	217	315	7783	634	60	910	2716	504	122	ND
92	38	ND	*	17175	21943	*	*	*	41369	48180	41369	29290	39909
94	49	12715	31135	4027	12718	45378	47863	2145	6249	423	*	727	ND
95	29	13137	32494	3468	30072	*	48552	4394	9716	466	*	2590	ND
97	51	16921	45845	6454	13569	*	*	25115	*	9716	*	10069	ND
98	38	14500	31693	1891	23236	*	*	2524	3788	592	*	1199	ND

\* = >50000

ND = Not determined

Table 10: Antagonist selectivity ratios determined for the human GAL3 receptor vs. alpha-adrenergic, dopamine, and histamine receptors.

Example	hGAL3	h $\alpha_{1A}$	h $\alpha_{1B}$	h $\alpha_{1D}$	h $\alpha_{2A}$	h $\alpha_{2B}$	h $\alpha_{2C}$	hD <sub>1</sub>	hD <sub>2</sub>	rD <sub>3</sub>	hD <sub>4</sub>	hD <sub>5</sub>	hH <sub>1</sub>
11	1	10	16	3	20	>100	>30	0.9	9	24	>30	0.7	ND
15	1	46	12	7	>100	>100	>100	5	30	>100	>30	1	ND
17	1	11	13	3	>30	>100	>100	6	21	28	>100	1	ND
22	1	>30	>30	13	>30	>100	>100	5	>30	>100	>100	2	ND
34	1	>100	>100	>30	>100	>100	>100	13	>100	>100	>100	5	ND
49	1	>30	>30	3	22	>100	>30	18	28	>30	>100	2	ND
60	1	>100	>100	>30	>100	>100	>30	7	>100	>100	>100	6	>100
77	1	11	6	3	4	>30	8	0.8	11	>30	6	2	ND
92	1	ND	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
94	1	>100	>100	>30	>100	>100	>100	>30	>100	9	>100	15	ND
95	1	>100	>100	>100	>100	>100	>100	>100	>100	16	>100	>30	ND
97	1	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	ND
98	1	>100	>100	>30	>100	>100	>100	>30	>100	16	>100	>30	ND

ND = Not determined

The activity of Example 92 was determined for central MAO<sub>A</sub> and central MAO<sub>B</sub> using the methods described hereinabove. The results, expressed as percent inhibition, are illustrated in Table 11.

5

Table 11: Percent inhibition of Example 92 in the central monoamine oxidase enzyme assay

TARGET	SPECIES	% INHIBITION
Monoamine Oxidase A (central)	Rat	10
Monoamine Oxidase B (central)	Rat	1

10

#### IV. GAL3 Receptor Localization

##### A. Materials And Methods

##### 5 Preparation of the anti-GAL3 Antiserum

BioSource International, Hopkinton, MA performed the immunization and maintenance of rabbits. Following a pre-immune bleed, one peptide for each GAL receptor was injected into a pair of New Zealand white rabbits. The  
10 peptide sequences was chosen based on sequence specificity and immunogenicity. The rabbit anti-GAL3 antiserum were raised against C-terminal epitopes corresponding to amino acids 357 - 370 (Genbank accession number AF073798). The peptides were conjugated to the  
15 carrier KLH (keyhole limpet hemocyanin) by a cross linker and subcutaneously injected into the rabbits. The generation of the anti-GAL3 antiserum required OVA followed by a third series of injections with the GAL3 peptide conjugated to tetanus toxoid (TTOX). All  
20 injections were done using the Freund's Adjuvant System. Once immunoreactivity was established (see below) the antiserum was affinity purified by passing it over an agarose based column, thiol coupled to its antigenic peptide. The column was washed and the antiserum was  
25 eluted using a low pH glycine buffer. The purified material was dialyzed, the optical density is taken at 280  $\lambda$  and the purified antiserum was frozen.

##### Characterization of the anti-GAL3 antiserum

30

##### Recombinant GAL1, GAL2, and GAL3 receptor transfected cells



To determine the ability of the GAL3 antiserum to recognize only the GAL3 receptor protein in vitro, COS-7 cells were grown on poly-L-lysine-coated plastic chamber slides (Nalge Nunc International, Naperville, IL) and  
5 transfected with recombinant rat GAL receptors (Genbank accession numbers U30290, AF010318, AF073798, respectively) or expression vector only (for mock-transfected cells) as previously described by Borowsky et al. (1999). Receptor expression was confirmed by  
10 radioligand binding. Briefly, a subset of slides was washed three times in binding buffer (50 mM Tris, pH 7.5, 5 mM MgCl<sub>2</sub>, 1 mM EDTA, 0.1% bovine serum albumin, and 0.1% bacitracin) and incubated in 500  $\mu$ l binding buffer containing porcine <sup>125</sup>I-galanin (625,000 dpm) plus or  
15 minus 10  $\mu$ M porcine galanin. After incubation at room temperature for 1 hour, the binding buffer was aspirated and slides were rinsed three times in ice cold 50 mM Tris, pH 7.5. Cells were solubilized in 1 ml of 0.1 N NaOH and 0.05% sodium deoxycholate for 30 minutes then  
20 transferred to test tubes for gamma counting of <sup>125</sup>I. To evaluate antibody activity another subset of slides were washed with phosphate buffered saline (PBS) (Sigma, St. Louis, MO) to remove the medium and fixed with 4% paraformaldehyde (PFA) (Sigma, St. Louis, MO) then  
25 permeabilized using 0.2% Triton X-100/PBS and incubated in 3% normal goat serum for 30 minutes to minimize nonspecific binding of the primary antibody. Cells were incubated overnight at 4°C with the anti-GAL3 antiserum (1:1000 dilution). The cells were rinsed three times with  
30 PBS, incubated for 30 minutes at 25°C with goat anti-rabbit IgG (1:200 dilution) (Santa Cruz Biotechnology, Santa Cruz, CA), rinsed and processed using the

peroxidase-antiperoxidase (PAP) reaction of Sternberger et al. (1982). Control experiments for antibody specificity were (1) incubation of the cells in primary antiserum that had been preabsorbed with the respective  
5 antigenic peptide (20 µg/ml), (2) incubation without the primary antiserum, or (3) incubation with the primary antiserum replaced by normal goat serum.

#### Western Blotting

10 Membranes were prepared from COS-7 cells transiently transfected with the rat recombinant receptors GAL1, GAL2, and GAL3 as previously described (Borowsky et al., 1999). Transfected cells were lysed by sonication in ice-cold sonication buffer (20 mM Tris-HCl, pH 7.7, 5 mM  
15 EDTA). Cell lysates were subjected to centrifugation at 4°C for 10 minutes at 200 g. The supernatant was then fractionated by centrifugation at 4°C for 18 minutes at 32,000 g. The resulting membrane pellet was suspended into 50 mM Tris, pH 7.5, 5 mM MgCl<sub>2</sub>, 1 mM EDTA. Protein  
20 samples (1-10 µg) were solubilized in 2 X Laemmli buffer (Bio-Rad, Hercules, CA) and fractionated by SDS-PAGE in 10% polyacrylamide gels. Proteins were transferred to polyvinylidene difluoride membranes for immunoblot analysis in ice-cold 25 mM Tris, pH 8, 192 mM glycine,  
25 20% methanol as previously described by Harlow and Lane (1999). Blots were incubated for 1 hour at 25°C in blocking buffer composed of 5% non-fat dried milk in TTBS (0.1% Tween-20, 500 mM NaCl, 20 mM Tris, pH 7.5) then for  
16 hours at 25°C with the receptor-specific polyclonal  
30 antibody (1:1000 dilution in blocking buffer) (0.25 mg/ml for GAL2 or 1.5 mg/ml for GAL3). Immunoreactive bands were detected with the Phototope-HRP Detection Kit for

Western Blotting (New England BioLab, Beverly, MA) according to the protocol. Briefly, the blots were incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG then developed with a mixture of LumiGLO plus hydrogen peroxide and recorded by chemiluminescence on Kodak Biomax-ML film (Kodak, Rochester, NY).

#### Immunohistochemistry

Male Sprague-Dawley rats, (200-250 g; Charles Rivers, Rochester, NY) were anesthetized by intraperitoneal injection of ketamine 20 mg/kg (RBI, Natick, MA) and xylazine 0.2 mg/kg (Bayer, Shawnee Mission, KS) then transcardially perfused with 200 ml PBS, pH 7.4 followed by 200 ml 4% PFA in PBS. The brains and spinal cords were removed, blocked, and postfixed in the same fixative for 4 hours at 4°C then cryoprotected in 30% sucrose in PBS at 4°C for 48 hours before freezing on dry ice. Coronal brain sections and transverse spinal cord sections were cut at 30  $\mu$ m using a freezing microtome. Tissue sections were immediately immersed in PBS and stored at 4°C until use. Sections were processed free-floating according to the protocol outlined in NEN Life Science Products TSA (Tyramide Signal Amplification) Indirect Kit. Briefly, tissue sections were permeabilized in 0.2% Triton X-100 (Sigma, St. Louis, MO)/PBS, incubated in 1% hydrogen peroxide (Sigma, St. Louis, MO)/PBS to remove endogenous peroxidase activity then blocked in TNB Buffer (0.1 M Tris-HCl, pH 7.5, 0.15 M NaCl, and 0.5% Blocking Reagent. Sections were incubated for 24 hours at 4°C in either the anti-GAL2 or anti-GAL3 antiserum (1:100). Following incubation with the primary antiserum, the tissue sections were washed in

TNT Buffer (0.1 M Tris-HCl, pH 7.4, 0.15 M NaCl, 0.05% Tween 20) followed by incubation at 25°C for 30 minutes with horseradish peroxidase (HRP)-conjugated goat anti-rabbit immunoglobulin (1:200) (Sternberger Monoclonals Inc., Lutherville, MD). Tissue sections were rinsed in TNT Buffer and incubated in a solution containing biotinylated tyramide to amplify the signal then rinsed in TNT buffer and incubated with HRP-conjugated to streptavidin at 25°C for 30 minutes. An immunoperoxidase reaction was done by incubating the section in 3,3'-diaminobenzidine (DAB) (0.05%) in 0.1 mM Tris, pH 7.4 and adding hydrogen peroxide to 0.006% immediately before use. The reaction was stopped in water and the sections mounted on microscopic slide with mounting medium (40% ethanol: gelatin) and counterstained with Cresyl violet then coverslipped for light microscopy.

Optimal GAL3 antibody concentrations (1:200) for rat brain sections were determined in preliminary titration experiments. Experimental controls in the tissue sections included (1) incubation in normal rabbit serum or (2) omission of the primary antiserum.

#### Analysis

COS-7 cells and tissue sections were examined using a Zeiss Axioscope. A total of 6 male rats were examined with the anti-GAL3 antiserum. The identification of GAL3-LI in the transfected cells and brain regions was based on the presence of immunoreactivity appearing as a brownish precipitate in individual cells and their projections or in the neuropil of the tissue by light

microscopy. The descriptions of neuroanatomic boundaries are based on the atlas of Paxinos and Watson (1998).

B. Results

5

Characterization of the GAL3 antiserum

Recombinant GAL1, GAL2, and GAL3 receptor transfected cells

10 The ability of the anti-GAL3 antiserum to recognize only the GAL3 receptor protein in vitro was established by performing immunocytochemistry on COS-7 cells transiently transfected with the recombinant receptor proteins for the rat GAL1, GAL2, and GAL3, or mock-transfected with  
15 vector only. Specific porcine <sup>125</sup>I-galanin binding was detected for all transfectants except mock-transfected cells. An immune response was detected only in the COS-7 cells incubated with the antiserum generated for the particular recombinant receptor. Specifically, no immune  
20 reaction was observed with the anti-GAL3 antiserum (1:1000) in GAL1 or GAL2 transfected cells. Furthermore, no visible immune reaction was detected in the mock-transfected cells. Incubation of the cells in primary antiserum that had been preabsorbed with the antigenic  
25 peptide (20 µg/ml) or without the primary antiserum or with the primary replaced by normal goat serum did not result in an immune response.

Taken together, these data demonstrate that the anti-GAL3  
30 antiserum recognizes the receptor against which it was generated and does not show cross reactivity with other known GAL receptors.

### Western Blots

To determine the specificity of the anti-GAL3 antiserum, COS-7 cells were transiently transfected either with recombinant rat GAL2 or GAL3 receptors or with expression vector only; membranes were then isolated for evaluation by immunoblotting (see Figure 5). The anti-GAL3 antiserum labeled proteins in membranes only from rat GAL3-transfected cells; a predominant band was evident with an apparent molecular weight of approximately 56 kDa (Figure 5), somewhat higher than the amino acid-derived value of 40.4 kDa. (For comparison, apparent molecular weights determined by SDS-PAGE are 56 kDa (Servin et al., 1987) or 54 kDa (Chen et al., 1992) for native GAL receptors purified from rat brain and 54 kDa (Amiranoff et al., 1989) for native GAL receptors purified from Rin m 5F cells. These values are all higher than the amino acid-derived value any known GAL receptor subtype, including the value of 38.9 kDa for rat GAL1 (Parker et al., 1995). The apparently high molecular weight observed for rat GAL3 very likely reflects post-translational processing such as glycosylation; note that rat GAL3 contains multiple N-terminal glycosylation sites (Smith et al., 1998). Relative to the predominant band, additional species of higher molecular weight as well as lower molecular weight were labeled by the corresponding antiserum (Figure 5). These are presumably receptor-related species composed of protein aggregates of C-terminal fragments, as they are absent in mock-transfected cells.

Immunohistochemical distribution of GAL3-LI in the CNS

GAL3-like immunoreactivity (GAL3-LI) was observed in many regions of the brain, specifically, the neocortex, septum, hippocampus, amygdala, and brainstem (see Table 12). Throughout the brain and spinal cord GAL3-LI was found to be associated with neuronal profiles however, there was neuropil staining observed in several brain regions. Several regions of the CNS almost exclusively expressed GAL3-LI, specifically the accumbens nucleus, dorsal raphe, ventral tegmental area (Table 12). There was no observable staining of the fiber tracts.

The specificity of the anti-GAL3 antiserum was determined in tissue sections by (1) omission of the primary antiserum or (2) incubation with normal rabbit serum. No specific staining was observed in either condition. Preabsorption of the GAL3 primary antiserum with the antigenic peptide (10 µg/ml) decreased but did not completely block staining in the tissue sections as in the transfected cells. This was most likely related to the different localization approaches. In the transiently transfected COS-7 cells the expression of GAL3 receptor protein was relatively high therefore, indirect immunocytochemistry with no amplification was used. In contrast, GAL3 receptor protein expression is presumed to be relatively lower in the tissue sections and for that reason the TSA (amplification) technique was employed. It is possible that because of the amplification (1000-fold) in the TSA technique even small amounts of unabsorbed antiserum may result in a signal.

Distribution of GAL3-LI in the rat CNSCerebral cortex

5 GAL3-LI was widespread in the cerebral cortex and the distribution pattern extended rostrocaudally. A weak to moderate GAL3-LI was seen in numerous cell bodies in the anterior cingulate cortex.

Septal region

10 An extensive and densely stained fiber network was seen throughout the entire lateral, intermediate and medial septal nuclei. The dorsal division of the lateral septum contained scarce moderately GAL3-like immunoreactive somata.

15

Basal ganglia

Numerous moderately GAL3-like immunoreactive cell bodies and fibers were present in the shell and core of the accumbens nucleus. The cell bodies of the subthalamic  
20 nucleus, a relay nucleus in the basal ganglia, contained weak GAL3-LI.

Amygdala and Extended Amygdala

In general, GAL3-LI was weak throughout the amygdala.  
25 Scattered cell bodies and fibers exhibited weak staining in several nuclei. Very fine GAL3-like immunoreactive fibers with scattered moderately labeled cells were detected in the central amygdaloid nucleus.

Midbrain/Mesencephalon

30 Labeled cells were detected within the dorsal raphe and projections from these cells were seen converging toward



the midline of the raphe. Moderately immunoreactive scattered cells were evident in the ventral tegmental area.

5 Brain stem

Intense staining was observed in cell bodies in the locus coeruleus.

10 The distribution of rat GAL3 protein in the CNS using  
receptor subtype selective polyclonal antibodies and  
tyramide signal amplification (TSA) immunocytochemistry  
is illustrated in Table 12. These were qualitative  
evaluations for the rat GAL3 receptor protein  
15 distribution based on the relative intensity of the  
chromogen (3,3'-diaminobenzidine) observed in individual  
cells at the microscopic level.

A total of 4 rat brains were analyzed for this study. As  
shown in Table 12, the strength of the signal obtained in  
20 various regions of the rat brain was graded as weak (+),  
or moderate (++) or intense(+++).

Table 12

REGION	cells	fibers	Potential Therapeutic Application
<b>Telencephalon</b>			
Frontal cortex	++		Anxiety/Depression
Cingulate cortex	++		Anxiety/Depression
<b>Basal ganglia</b>			
Accumbens nucleus	++	-	Treatment of the positive symptoms of schizophrenia Treatment of drug addiction. This region is particularly sensitive to psychoactive drugs. Anxiety/depression
<b>Septal Region</b>			Relief of fear
Lateral septal nucleus, dorsal	+	++	
Lateral septal nucleus, ventral	+	++	
Intermediate septal nucleus	-	++	
Medial septal nucleus		++	
<b>Amygdala and extended Amygdala</b>			Treatment of anxiety, panic attack, and depression. Treatment of disorders of integrated behaviors such as defense, ingestion, reproduction, and learning.
Central nucleus	++	++	Fear and anxiety

<b>Mesencephalon</b>			
Dorsal raphe	++	-	Depression/Analgesia
Ventral tegmental area	++	-	Depression
<b>Brainstem/Pons/Medulla</b>			
Locus coeruleus	+++	-	Modulation of noradrenergic transmission. Treatment of depression

The GAL3 antiserum was characterized using recombinant GAL receptors in transiently transfected COS-7 cells and Western blot analysis and the specificity of the GAL3 antiserum to recognize only the cognate receptor in vitro was established. The anatomical distribution of the GAL3 receptor protein in the rat CNS was determined using a modified immunohistochemical technique to enhance sensitivity and detectability via tyramide signal amplification (Toda et al., 1999).

The results indicate that the expression GAL3-LI was primarily found in neuronal profiles with neuropil labeling detectable in several areas. In general, the distribution of GAL3-LI is in good agreement with the reported distribution for galanin-LI, galanin binding sites, and GAL3 mRNA in the rat brain (for recent review, Branchek et al., 2000). Overall, GAL3-LI was extensively distributed throughout the brain. Paralleling the distribution of galanin binding sites GAL3-LI was observed in ventral regions of the brain.

The localization of the GAL3 protein in the dorsal raphe and locus coeruleus suggests a potential therapeutic application of galanin receptor antagonists in the treatment of depression by attenuating galanin's  
5 inhibitory tone on both of these regions.

A decrease in central serotonin (5-HT) neurotransmission has been implicated in depression. GAL3 antagonists could possibly act via GAL3 receptors on the cell bodies of  
10 dorsal raphe neurons to increase firing rate of raphe neurons thus increasing 5-HT release in the telencephalon and diencephalon. Another possible site of action for a GAL3 antagonist could be on postsynaptic GAL3 receptors in the limbic forebrain to block the putative ability of  
15 galanin to negatively regulate 5-HT<sub>1A</sub> receptor transmission (Misane et al, 1998).

Unlike the dorsal raphe cells, the cells of the locus coeruleus express abundant galanin under normal  
20 conditions and it has been proposed that galanin may be released from dendrites and soma of the noradrenergic cell bodies (for review, Hökfelt et al., 1998). The ascending afferent projections of the locus coeruleus are extensive throughout the brain. Changes in the  
25 noradrenergic system have been hypothesized to be involved in depression-related behaviors and symptoms (for review, Weiss et al., 1998). The ventral tegmental area (VTA) receives projections from the locus coeruleus that have been reported to co-localize galanin and  
30 noradrenaline. It has been proposed that in certain pathological states (ex. stress induced depression) galanin released from noradrenergic terminals in the VTA

inhibits dopaminergic neurons in the region that results in decreased dopamine release in the forebrain regions, particularly the accumbens nucleus and prefrontal cortex. This decrease in dopamine release produces a decreased  
5 motor activation and anhedonia. GAL3 has been identified in all of these regions and thus presents itself as a potential therapeutic target in the treatment of depression. Drugs that would effectively decrease galanin's release in the VTA whether at the level of the  
10 locus coeruleus (somatodendritic GAL3 receptors to decrease the activity of LC cells) or in the VTA itself (presynaptically on NE/GAL terminals in the VTA or via GAL3 receptors on VTA-DA neurons to prevent the hyperpolarization VTA-DA cells by released galanin) would  
15 produce an antidepressant effect.

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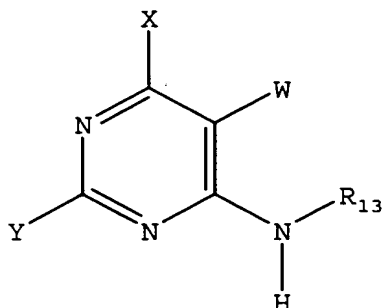
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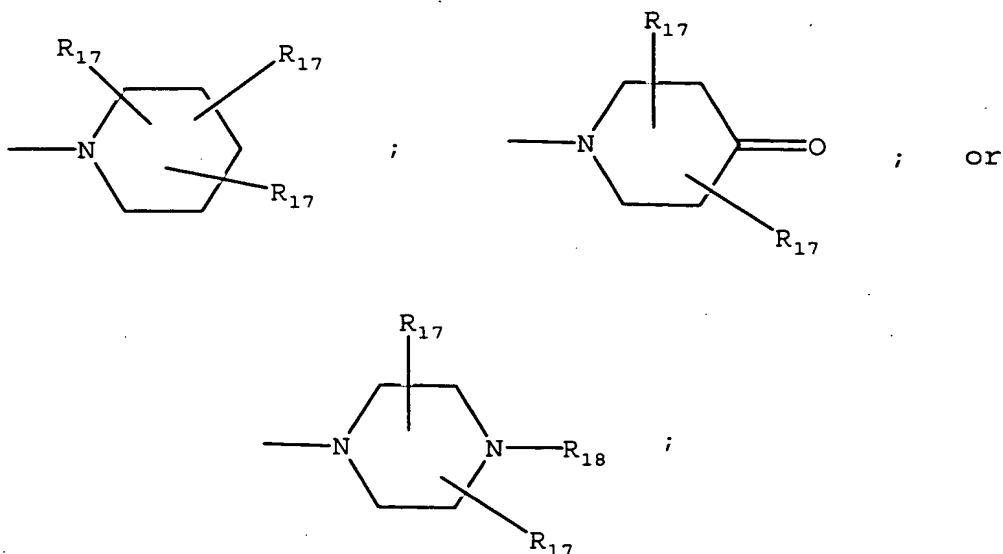
1. A method of treating a subject suffering from depression which comprises administering to the subject  
 5 an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

10

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

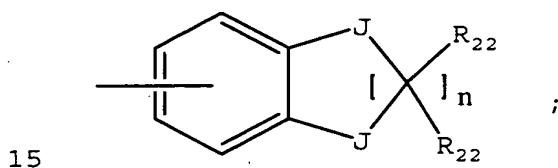


wherein  $R_{12}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ , or  $-(CH_2)_m-Z$ ;

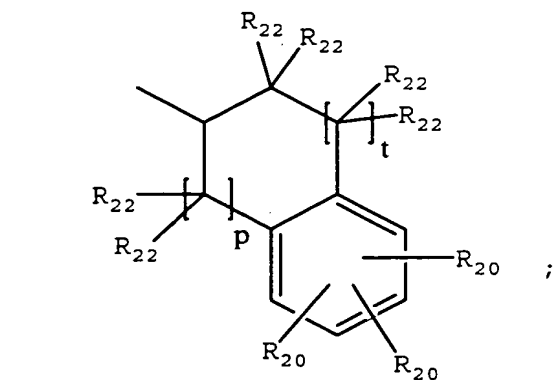
- 5 wherein  $R_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl, aryl, aryl( $C_1$ - $C_6$ )alkyl,  $Q_1$  or  $Q_2$ ;

wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$   
 10 straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is



wherein  $Q_2$  is

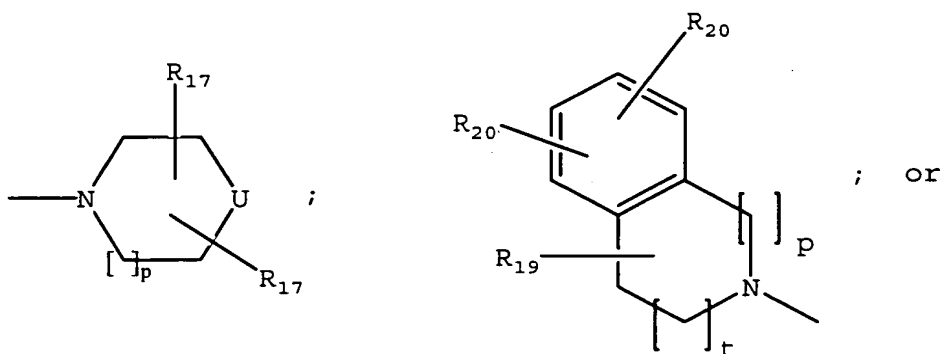


wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



10

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15 wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl,  $(C(R_{19})_2)_mN(R_{16})_2$  or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  
20 straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl,

straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

5

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

10

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl;  $-F$ ,  $-Cl$ ,  $-Br$ , or  $-I$ ;  $-NO_2$ ;  $-N_3$ ;  $-CN$ ;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

20

25

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl, or aryl( $C_1-$

30

C<sub>6</sub>)alkyl;

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

5

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

10 wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

15

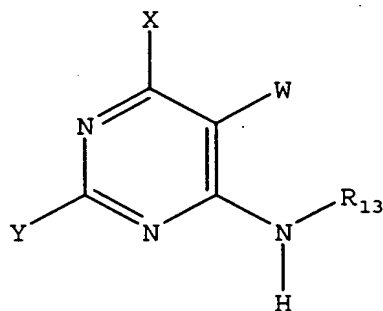
wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

wherein Z is C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>4</sub>-C<sub>7</sub> cyclic ether, C<sub>4</sub>-C<sub>7</sub> cyclic thioether, aryl, or heteroaryl; or

20

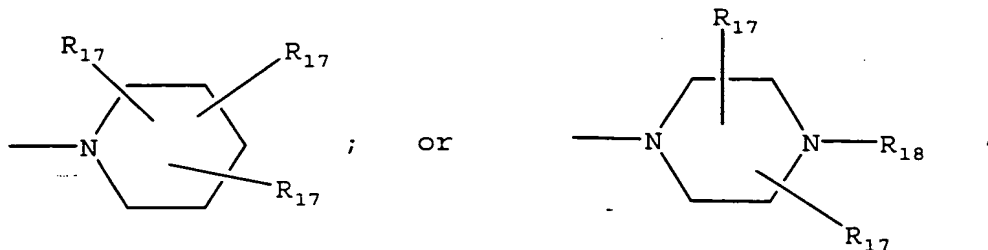
a pharmaceutically acceptable salt thereof.

2. A method of treating a subject suffering from  
25 depression which comprises administering to the subject  
an amount of compound effective to treat the subject's  
depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5. wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



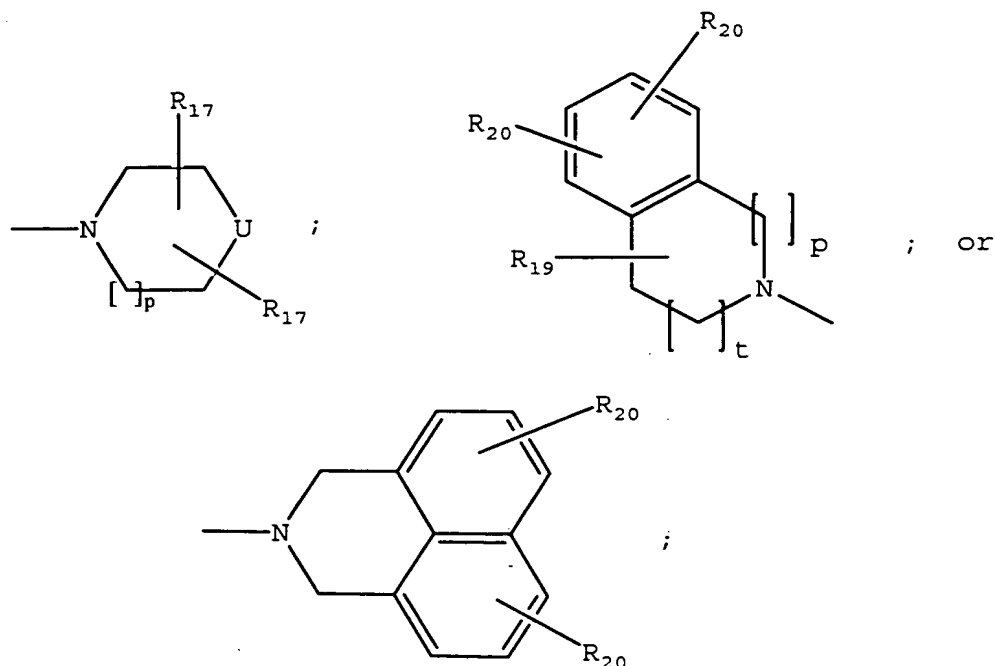
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

- 10 wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

- 15

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein R<sub>14</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

5

wherein R<sub>15</sub> is straight chained or branched C<sub>3</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

10

wherein Z is C<sub>3</sub>-C<sub>10</sub> cycloalkyl, aryl, or heteroaryl;

wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, - (CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{15}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

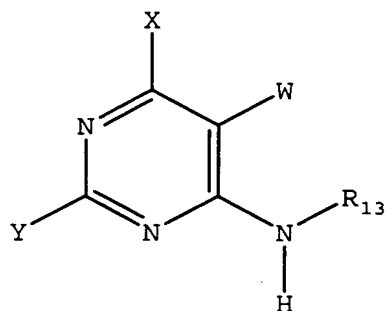
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

3. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

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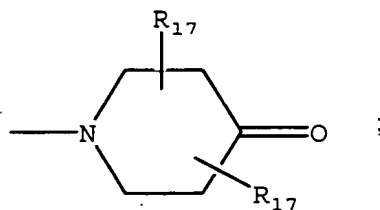


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20

wherein X is N(CH<sub>3</sub>)<sub>2</sub> or



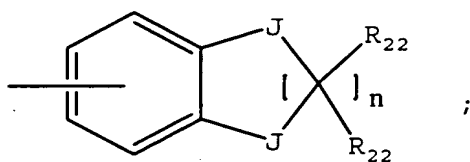


wherein  $\text{R}_{13}$  is an aryl, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl,  $\text{Q}_1$  or  $\text{Q}_2$ ;

5

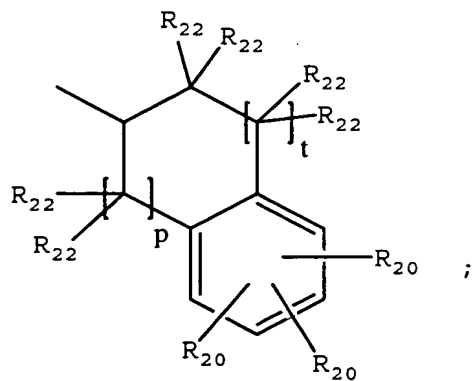
wherein aryl may be substituted with one or more  $\text{C}_1\text{-C}_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $\text{N}(\text{R}_{19})\text{-Z}$ ;

10 wherein  $\text{Q}_1$  is



wherein  $\text{Q}_2$  is

15

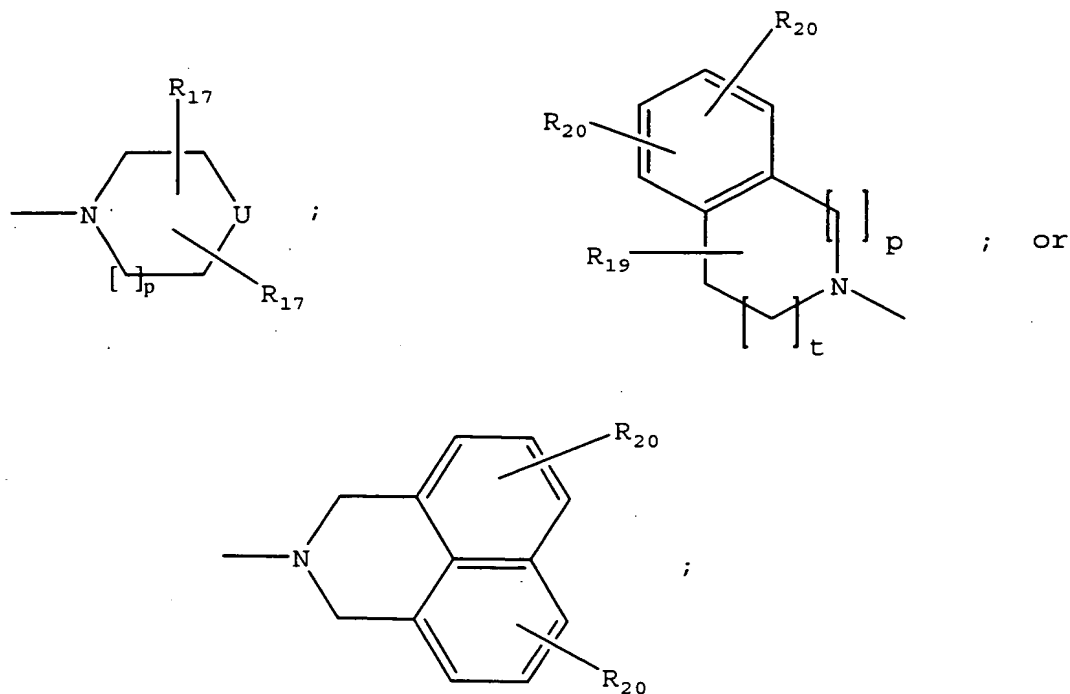


wherein each J is independently O, S,  $\text{C}(\text{R}_{22})_2$  or  $\text{NR}_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



- 10 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

15

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl,  
 5 straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 10  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$   
 15 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20 wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently  $-H$ ; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 25 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl;  $-F$ ,  $-Cl$ ,  $-Br$ , or  $-I$ ;  $-NO_2$ ;  $-N_3$ ;  $-CN$ ;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to  
 30 form a methylenedioxy group;

wherein each  $R_{21}$  is independently  $-H$ ; straight chained or

branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-  
 C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-  
 C<sub>6</sub>)alkyl;

5

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub>  
 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

10

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

15

wherein q is an integer from 2 to 4 inclusive;

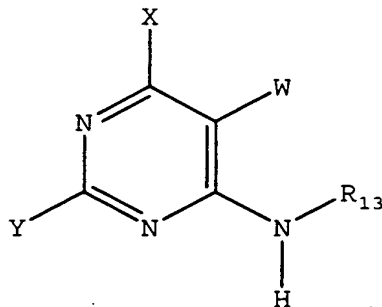
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

4. A method of treating a subject suffering from  
 depression which comprises administering to the  
 subject an amount of compound effective to treat the  
 subject's depression wherein the compound has the  
 structure:

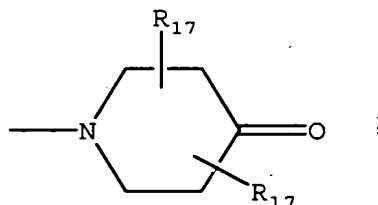
25



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5

wherein X is  $N(CH_3)_2$  or



10 wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein Y is  $NR_{14}R_{15}$ ;

15 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

20 wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, 25 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,

-NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

10

wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

15

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

20

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

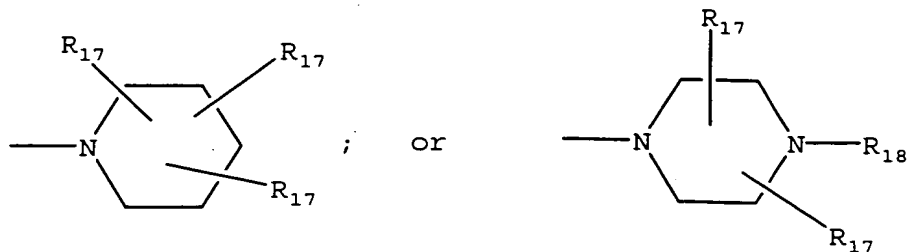
25 5. The method of claim 1, 2, 3 or 4, wherein the compound is enantiomerically and diasteriomERICALLY pure.

6. The method of claim 1, 2, 3 or 4, wherein the compound is enantiomerically or diasteriomERICALLY pure.

30

7. The method of claim 1, 2, 3 or 4, wherein the compound can be administered orally.

8. The method of claim 1, wherein X is:

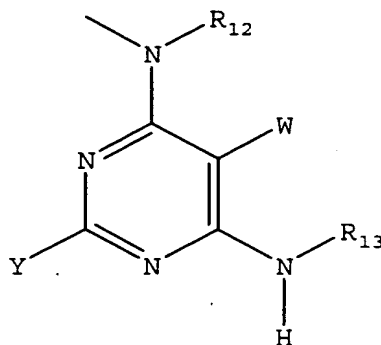


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9. The method of claim 1, wherein X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

10. The method of claim 9, wherein the compound has the structure:

10



11. The method of claim 8, wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.

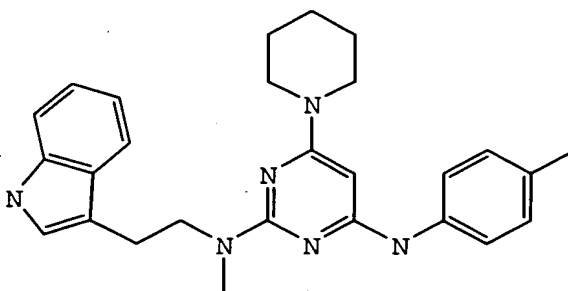
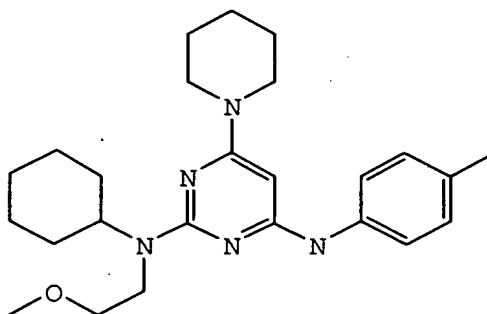
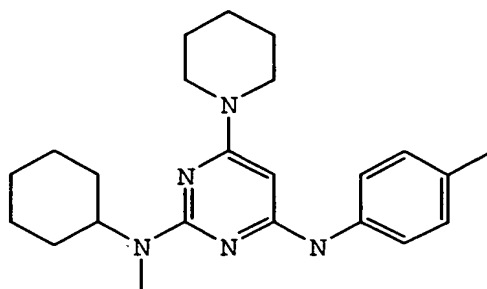
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12. The method of claim 10, wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.

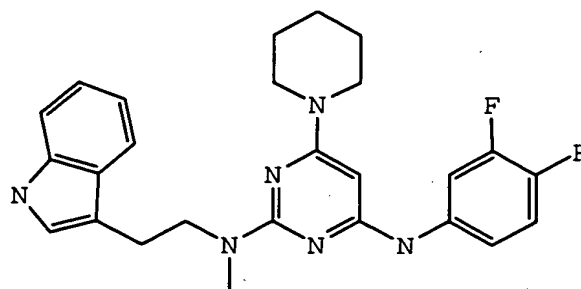
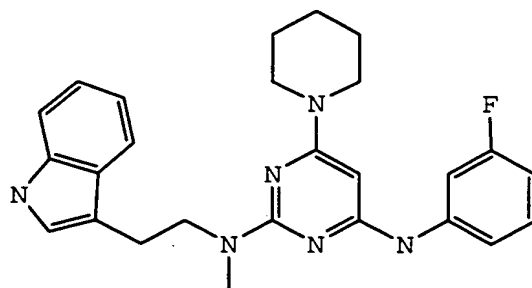
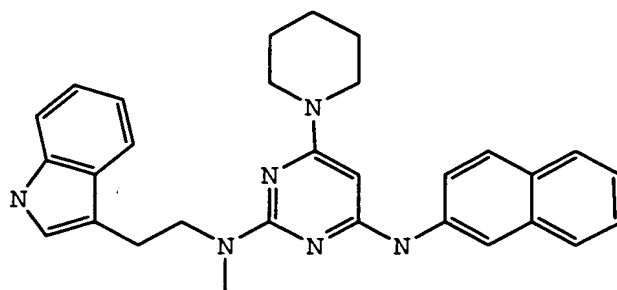
13. The method of claim 11, wherein  $\text{R}_{14}$  is H, straight  
20 chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ .

14. The method of claim 12, wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl or  $(CH_2)_q-O-(CH_2)_m-CH_3$ .

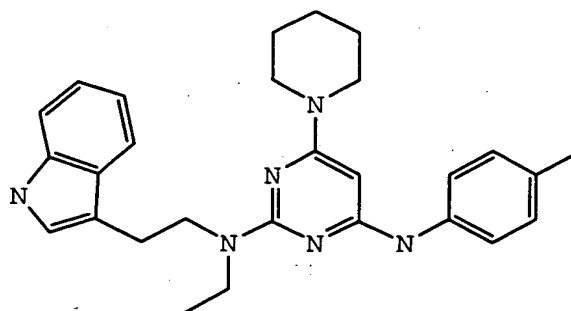
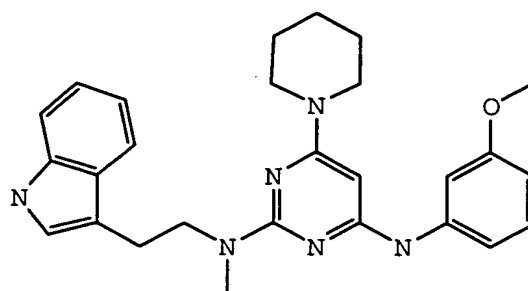
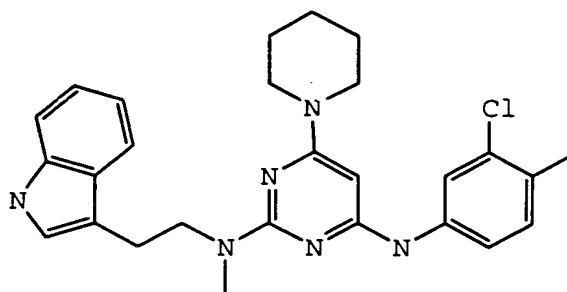
5 15. The method of claim 13, wherein the compound is selected from the group consisting of:

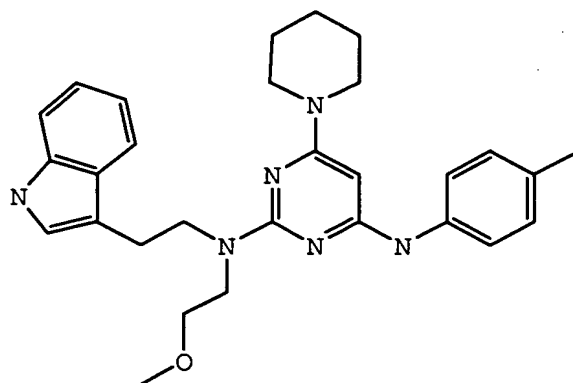




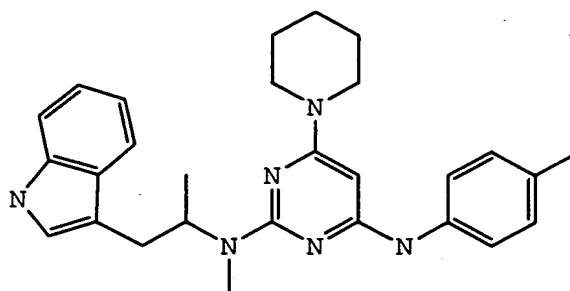


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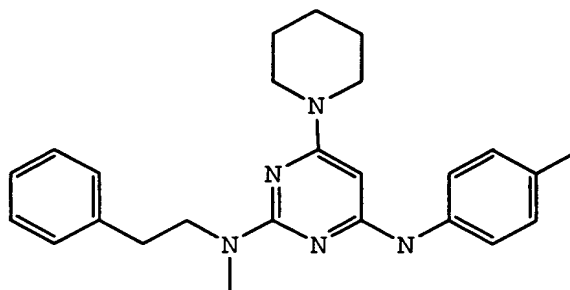




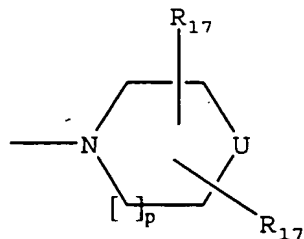
;



; and



16. The method of claim 11, wherein Y is



17. The method of claim 16, wherein U is  $\text{NR}_{16}$ .

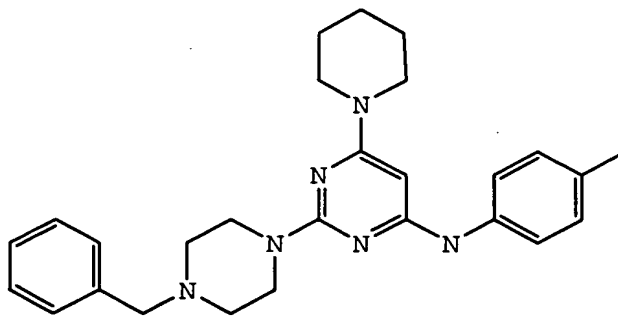
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18. The method of claim 17, wherein  $\text{R}_{16}$  is  $(\text{CH}_2)_m\text{-Z}$ .

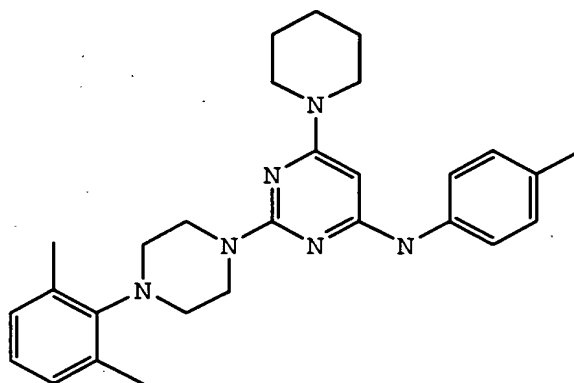
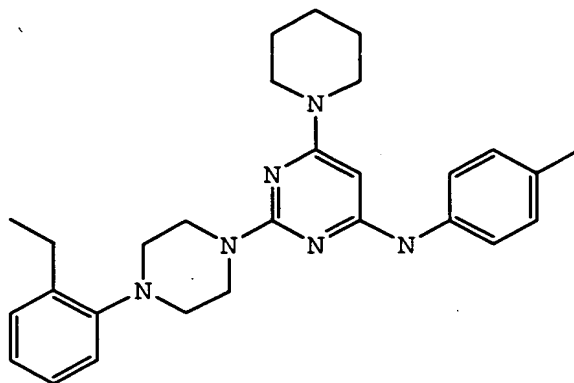
19. The method of claim 18, wherein Z is aryl or heteroaryl.

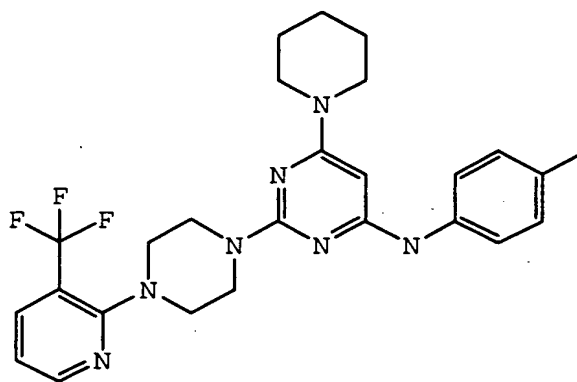
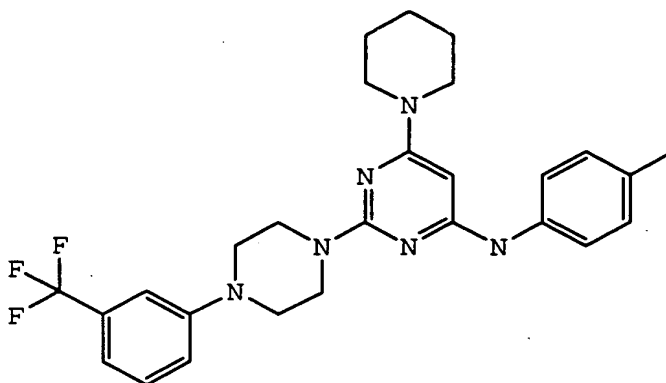
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20. The method of claim 19, wherein the compound is selected from the group consisting of:

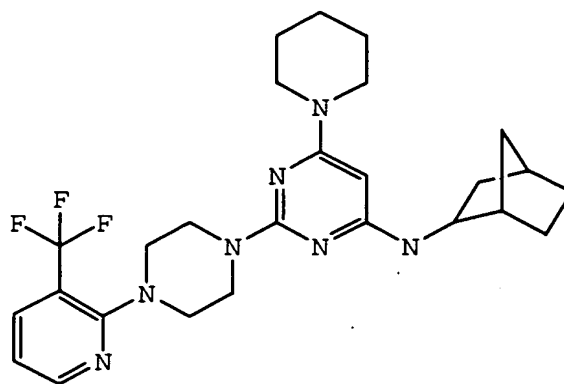


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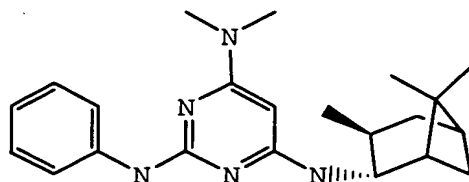
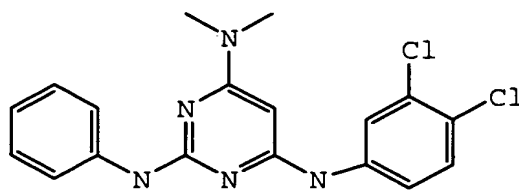
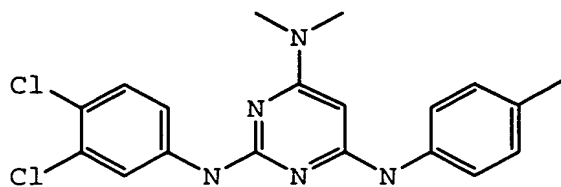


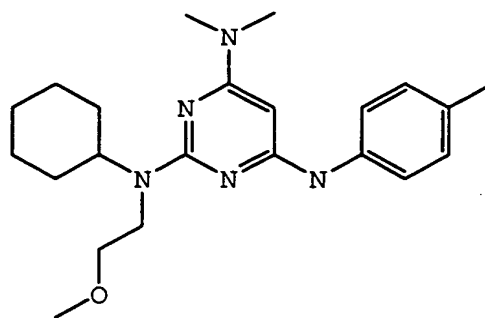


; and

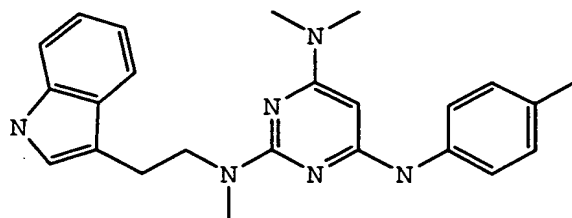


21. The method of claim 12, wherein the compound is selected from the group consisting of:

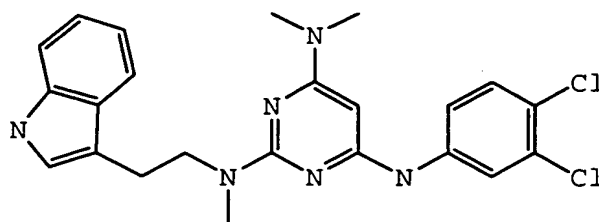




;

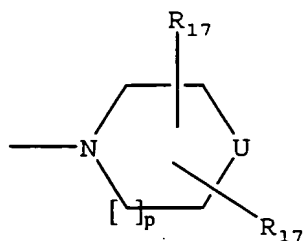


; and



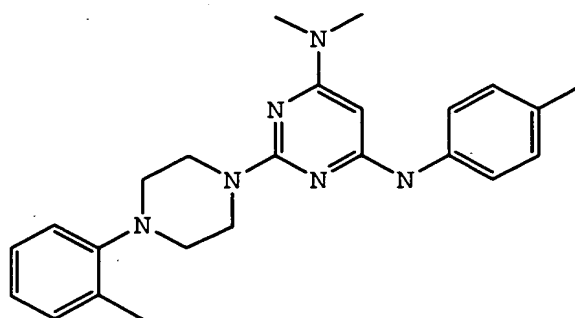


22. The method of claim 12, wherein Y is

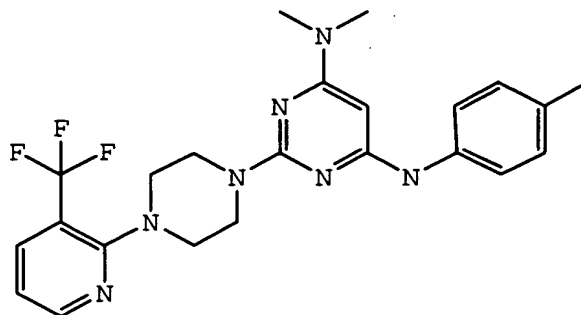


23. The method of claim 22, wherein  $U$  is  $NR_{16}$ .

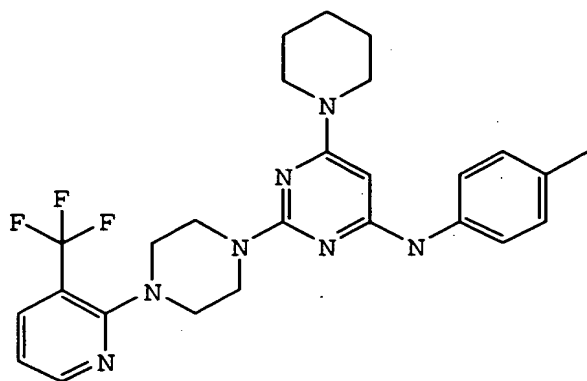
24. The method of claim 23, wherein the compound is



; or

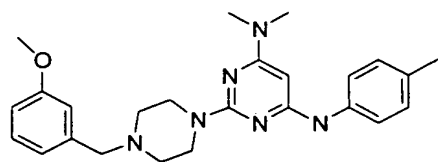


25. The method of claim 19, wherein the compound is

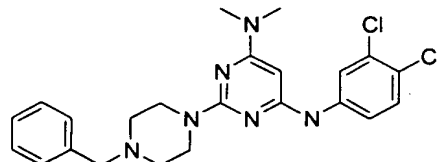


26. The method of claim 23, wherein the compound is selected from the group consisting of:

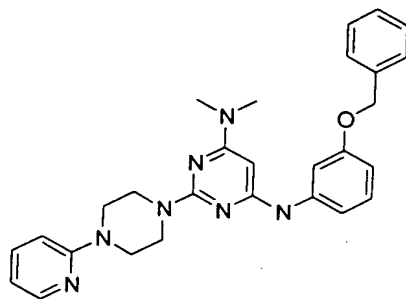
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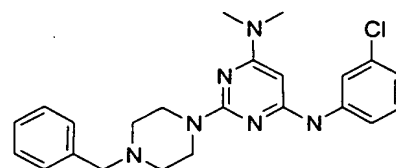
;



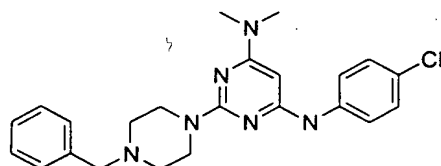
;



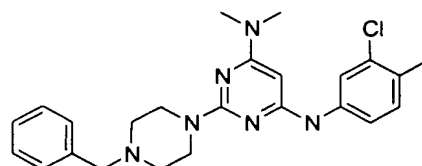
;



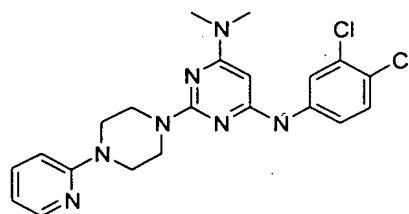
;



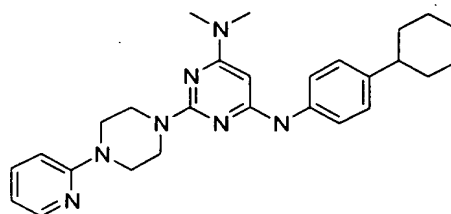
;



;

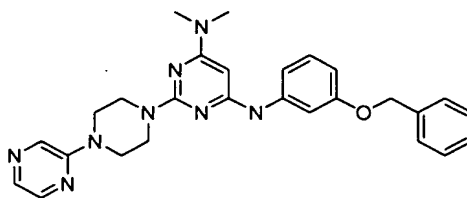
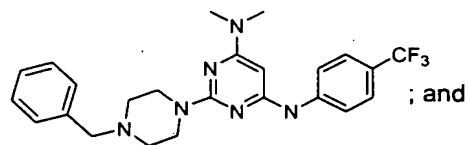
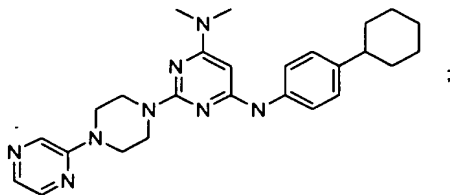
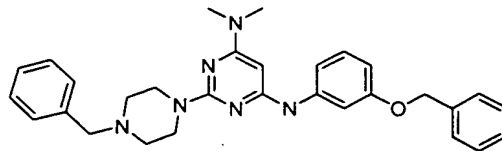
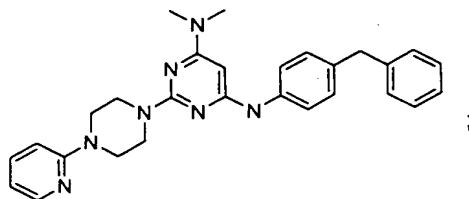
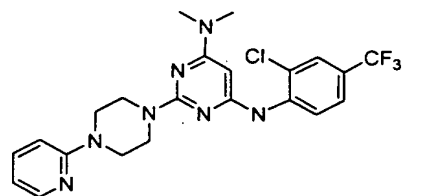
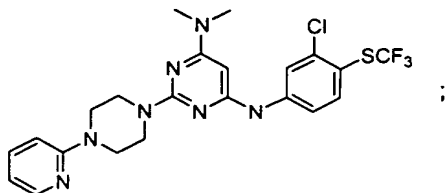
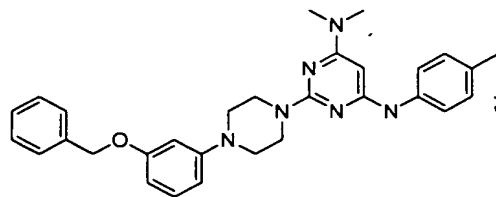
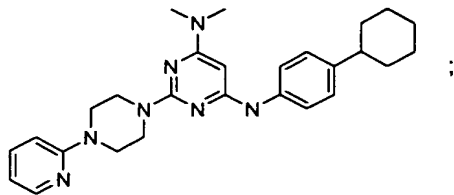


;and



10

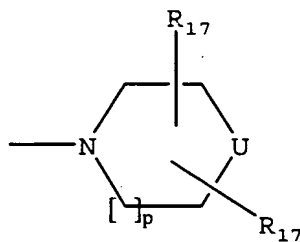
27. The method of claim 23, wherein the compound is selected from the group consisting of:



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28. The method of claim 3, wherein X is  $N(CH_3)_2$ .

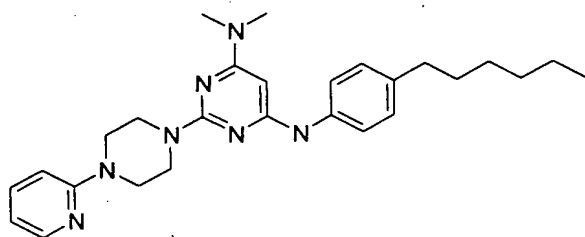
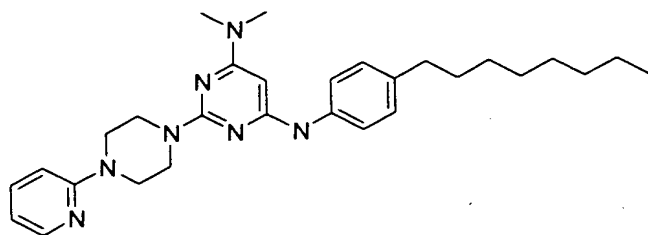
29. The method of claim 28, wherein Y is



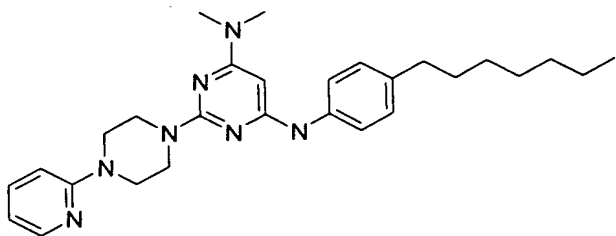
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30. The method of claim 29, wherein  $R_{13}$  is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained alkyl.

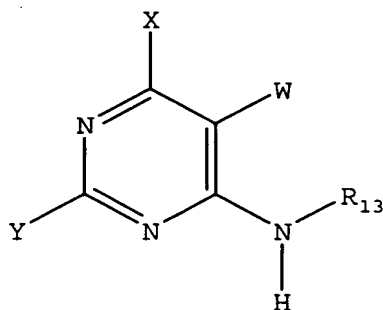
31. The method of claim 30, wherein the compound is selected from a group consisting of:



; and



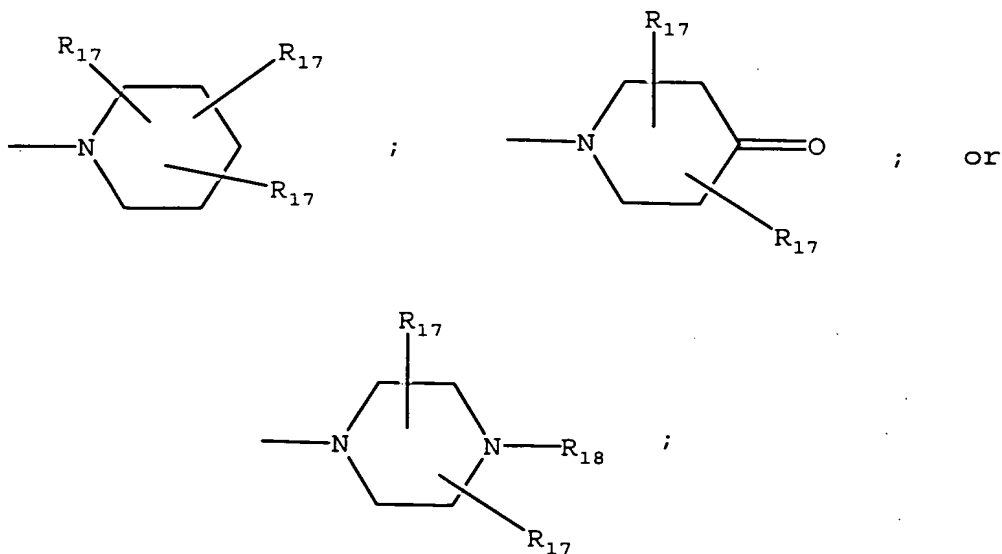
32. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



5

wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



10

wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,

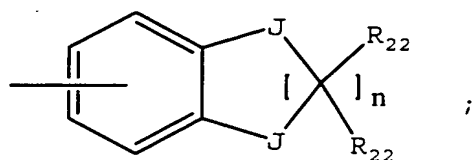
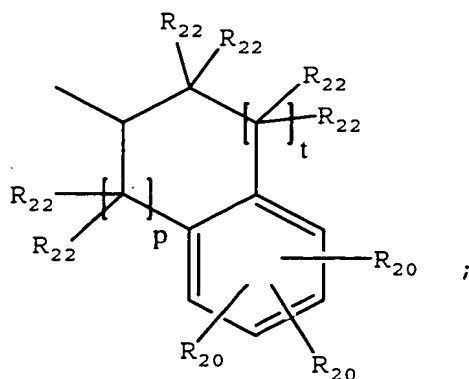
$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $\text{C}_3\text{-C}_{10}$  cycloalkyl, heteroaryl, aryl, aryl( $\text{C}_1\text{-C}_6$ )alkyl,  $\text{Q}_1$  or  $\text{Q}_2$ ;

wherein aryl may be substituted with one or more  $\text{C}_1\text{-C}_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $\text{N}(\text{R}_{19})\text{-Z}$ ;

10

wherein  $\text{Q}_1$  is

15 wherein  $\text{Q}_2$  is

wherein each J is independently O, S,  $\text{C}(\text{R}_{22})_2$  or  $\text{NR}_4$ ;

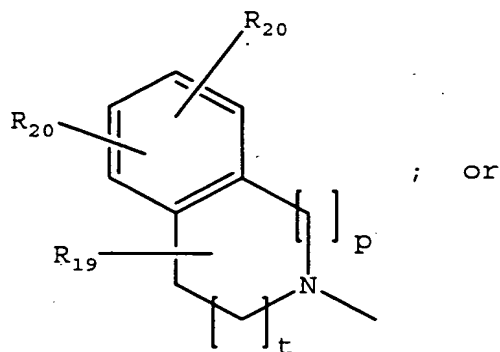
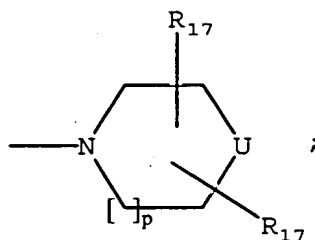
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wherein  $\text{R}_4$  is H; straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or

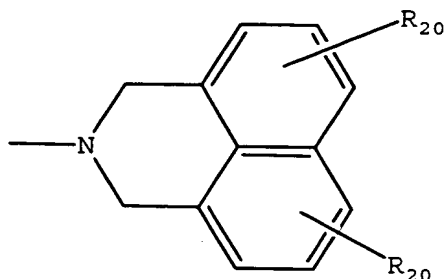


branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl or aryl;

wherein Y is NR<sub>14</sub>R<sub>15</sub>;



5



10 wherein R<sub>14</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

wherein R<sub>15</sub> is straight chained or branched C<sub>3</sub>-C<sub>6</sub> alkyl, (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>N(R<sub>16</sub>)<sub>2</sub> or  
15 (C(R<sub>19</sub>)<sub>2</sub>)<sub>m</sub>-Z;

wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl,  
20 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight

chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 5  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or  
 branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$   
 monofluoroalkyl, straight chained or branched  $C_1-C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2-C_7$   
 alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$   
 10 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15 wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $C_1-C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or  
 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 20 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$   
 cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  
 -NO<sub>2</sub>; -N<sub>3</sub>; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  
 $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups  
 present on adjacent carbon atoms can join together to  
 25 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or  
 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$   
 30  $C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl, or aryl( $C_1-C_6$ )alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10 wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

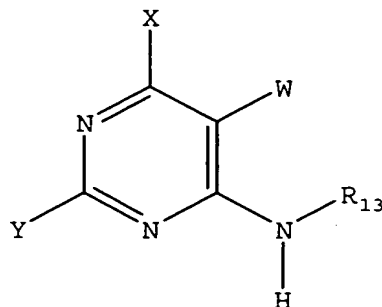
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wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

a pharmaceutically acceptable salt thereof.

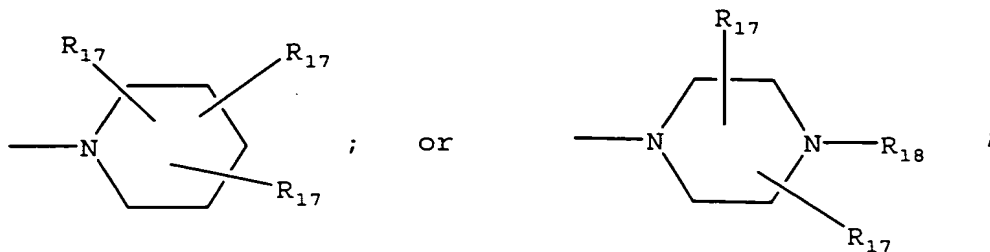
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33. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's  
25 anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



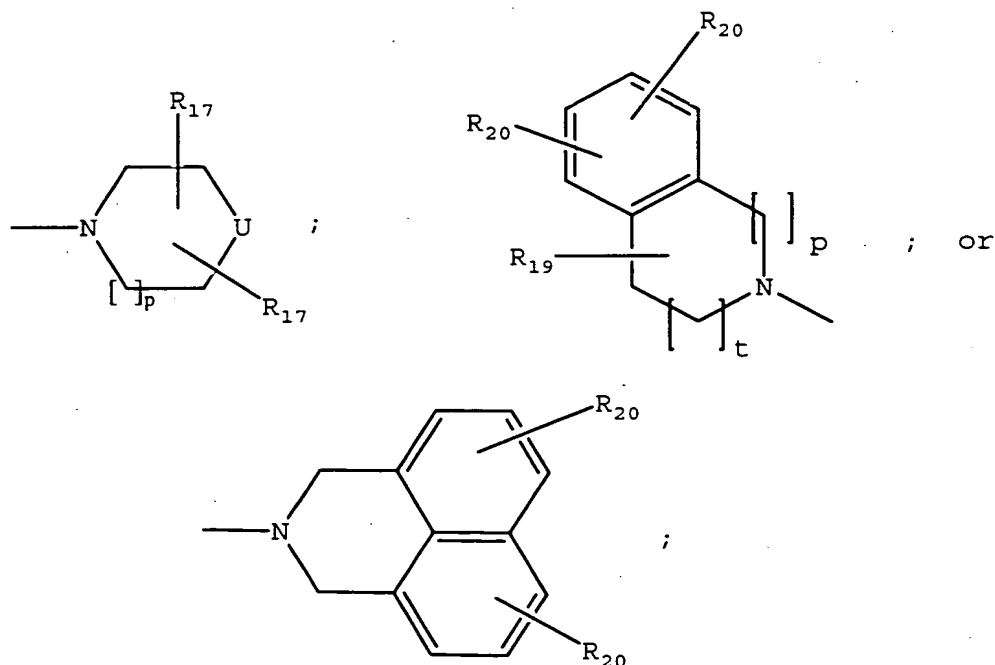
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wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 10  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

15 wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

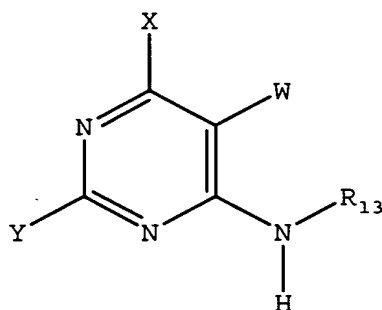
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

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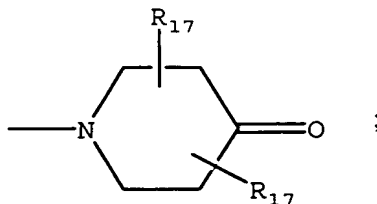
34. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20 wherein X is  $N(CH_3)_2$  or

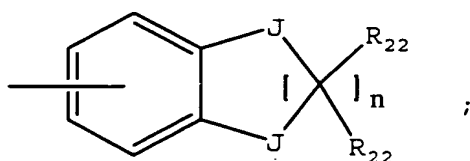


wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

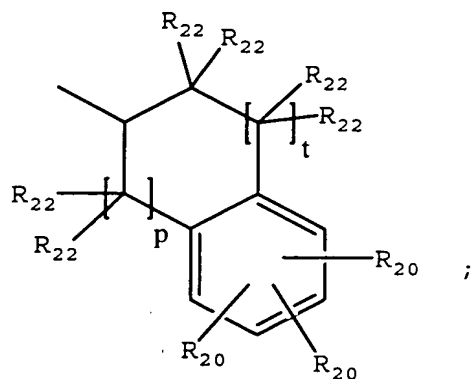
- 5 wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is

10



wherein  $Q_2$  is



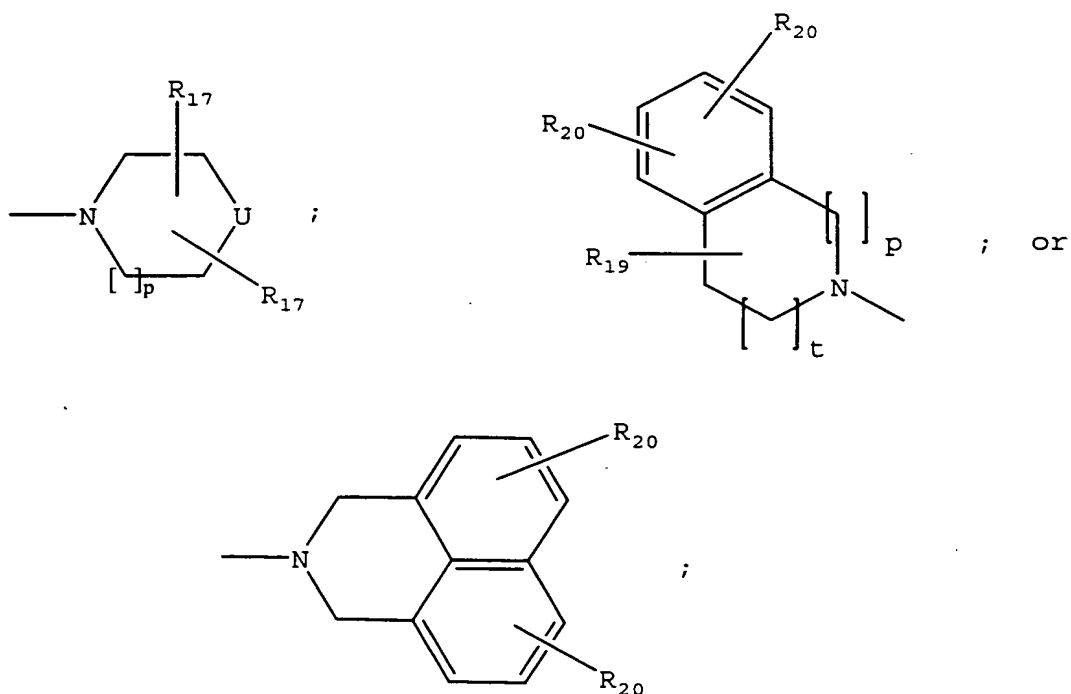
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wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

- wherein  $R_4$  is  $-H$ ; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight  
 20 chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;



wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  
 10  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein U is O,  $\text{-NR}_{16}$ , S,  $\text{C}(\text{R}_{17})_2$ , or  $\text{-NSO}_2\text{R}_{16}$ ;

wherein Z is  $\text{C}_3\text{-C}_{10}$  cycloalkyl, aryl, or heteroaryl;

15

wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl,

straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

- 5 wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;
- 10

wherein  $R_{18}$  is straight chained or branched  $C_1-C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

- wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;
- 20
- 25

- wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;
- 30

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

10 wherein q is an integer from 2 to 4 inclusive;

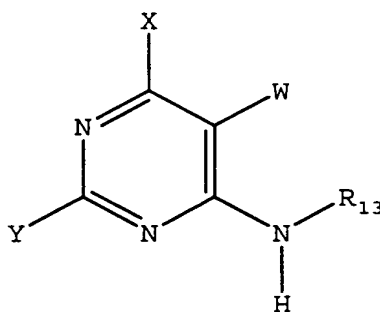
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

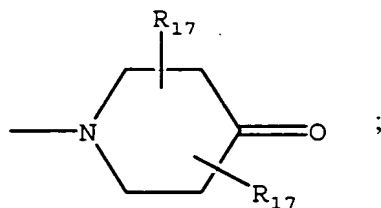
35. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

20



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

25 wherein X is  $N(CH_3)_2$  or



wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

5

wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

10

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

15 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
20  $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$   
25 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

5 wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

10

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

15 wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

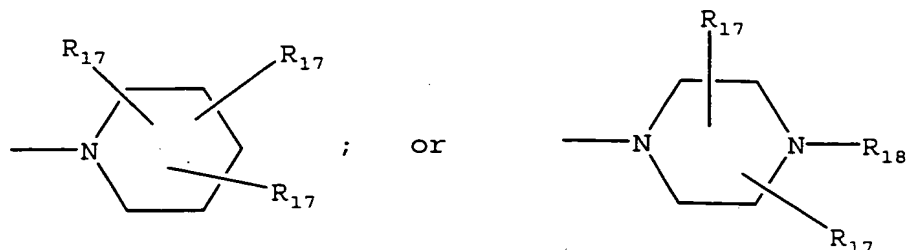
20 36. The method of claim 32, 33, 34 or 35, wherein the compound is enantiomerically and diasteriomERICALLY pure.

25 37. The method of claim 32, 33, 34 or 35, wherein the compound is enantiomerically or diasteriomERICALLY pure.

38. The method of claim 32, 33, 34 or 35, wherein the compound can be administered orally.

30

39. The method of claim 32, wherein X is:

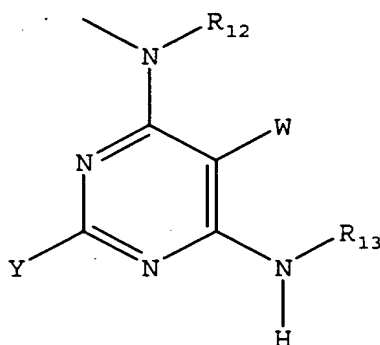


5

40. The method of claim 32, wherein X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

41. The method of claim 40, wherein the compound has the structure:

10



42. The method of claim 39, wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.

15

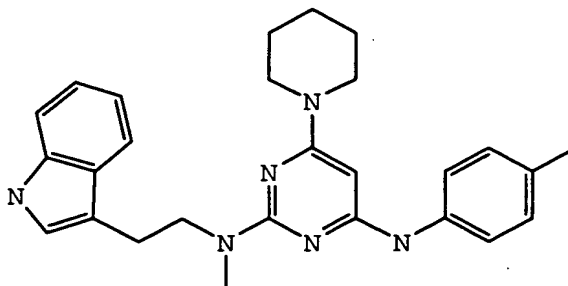
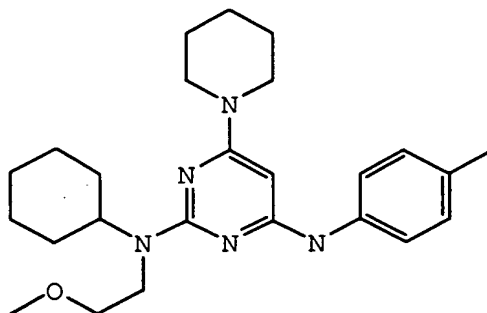
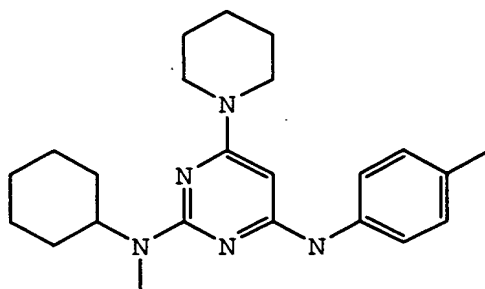
43. The method of claim 41, wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.

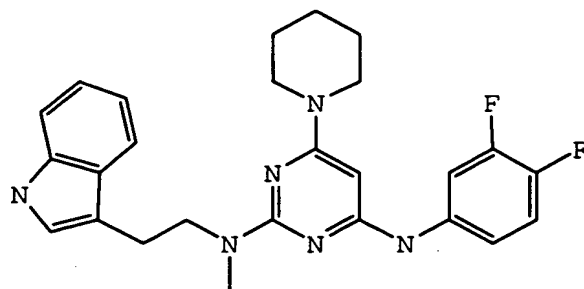
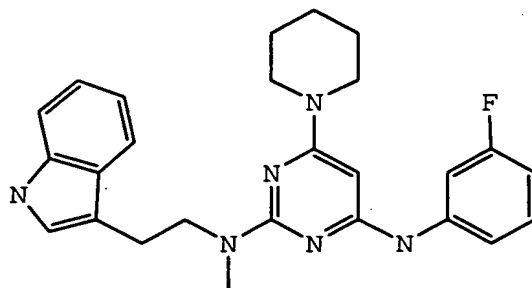
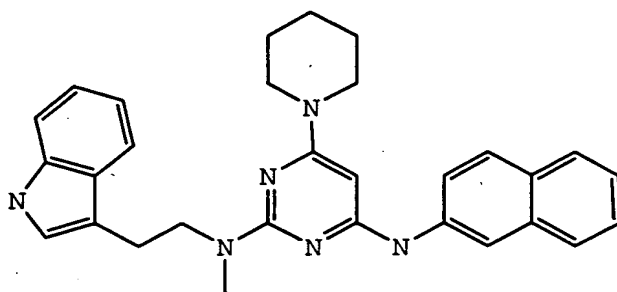
44. The method of claim 42, wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

20

45. The method of claim 43, wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl or  $(CH_2)_q-O-(CH_2)_m-CH_3$ .

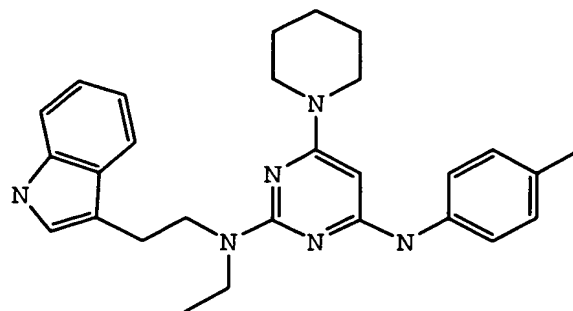
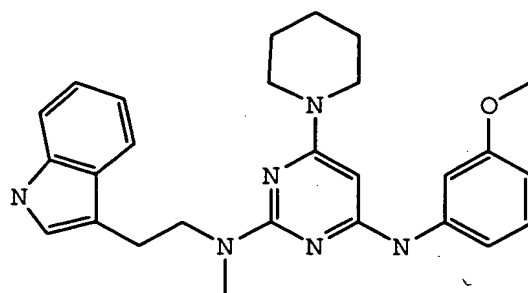
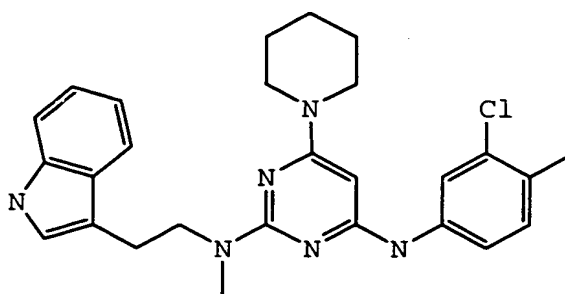
5 46. The method of claim 44, wherein the compound is selected from the group consisting of:

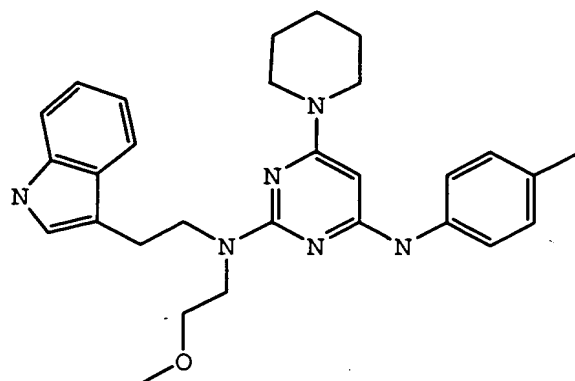




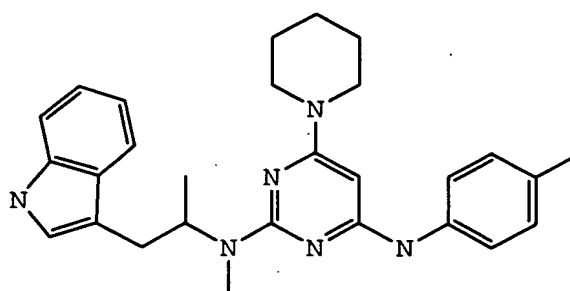


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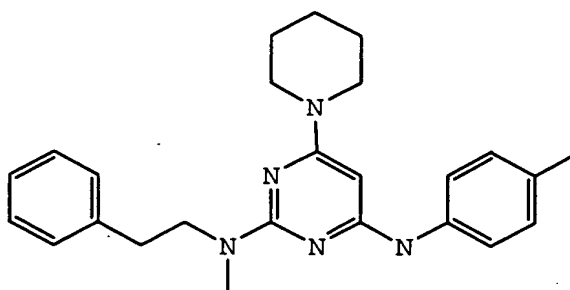




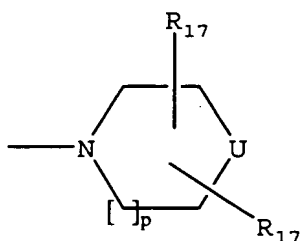
;



; and



47. The method of claim 42, wherein Y is

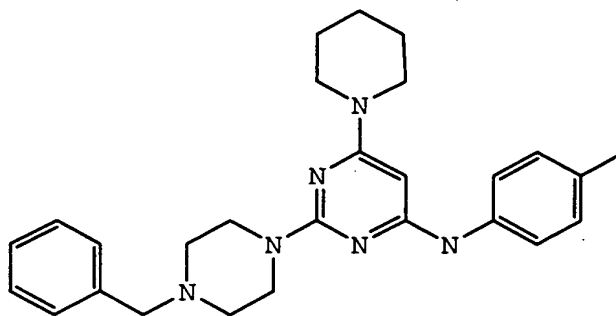


5 48. The method of claim 47, wherein U is  $\text{NR}_{16}$ .

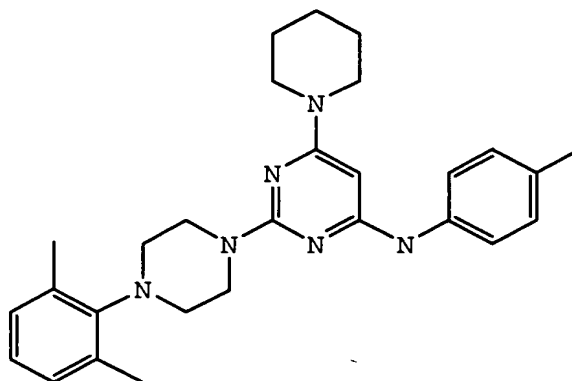
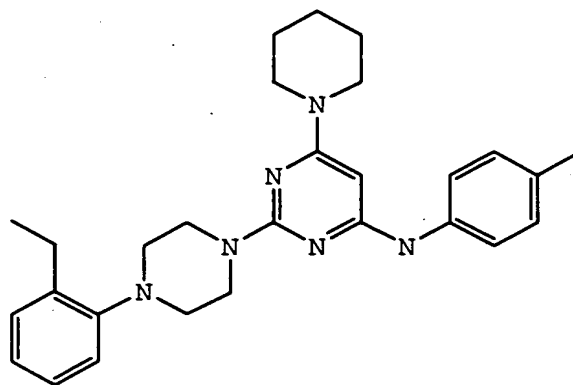
49. The method of claim 48, wherein  $\text{R}_{16}$  is  $(\text{CH}_2)_m\text{-Z}$ .

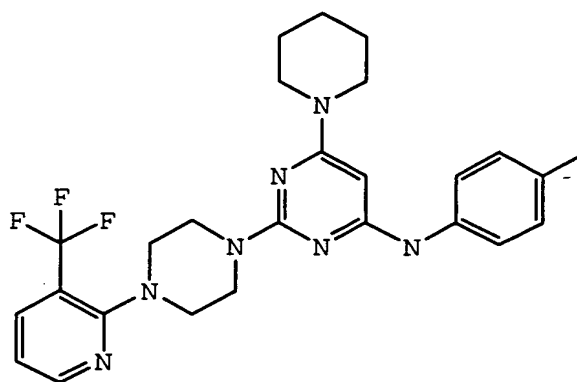
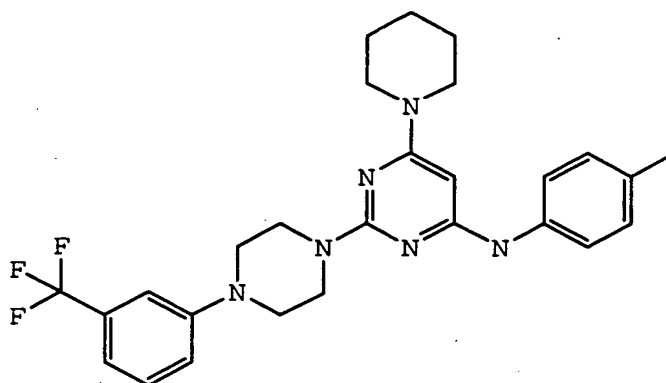
50. The method of claim 49, wherein Z is aryl or  
10 heteroaryl.

51. The method of claim 50, wherein the compound is selected from the group consisting of:

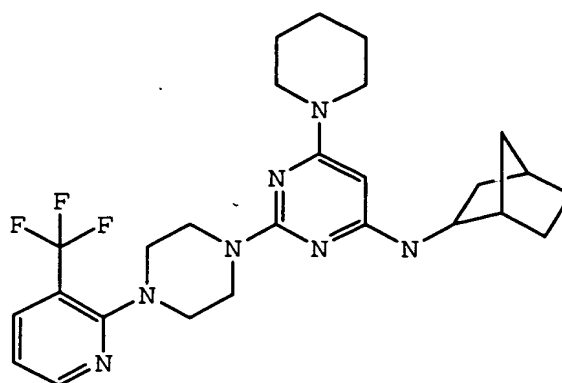


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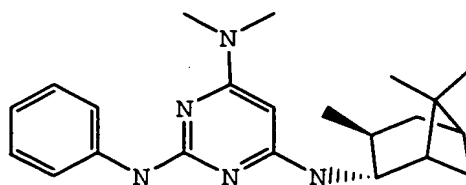
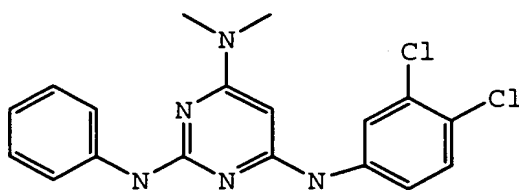
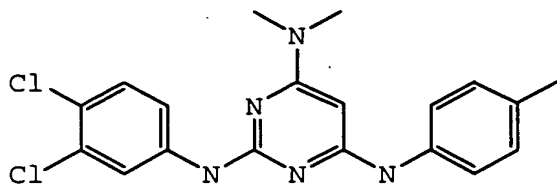


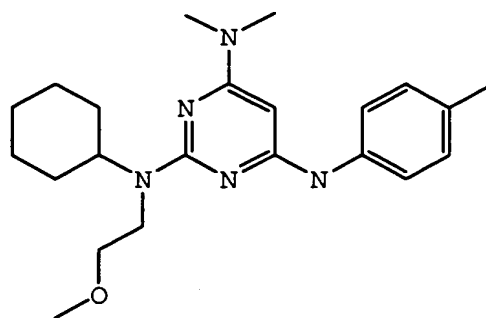


; and

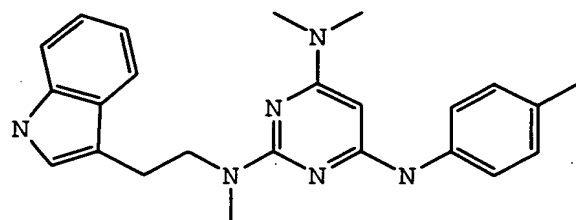


52. The method of claim 43, wherein the compound is selected from the group consisting of:

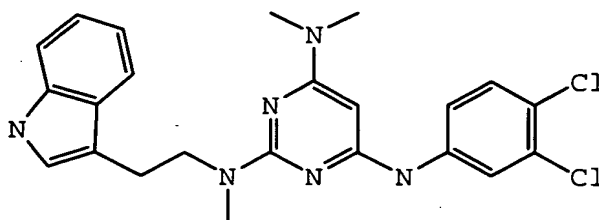




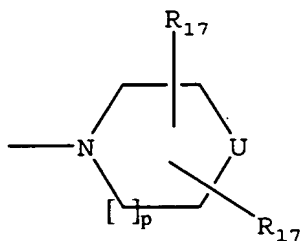
;



; and

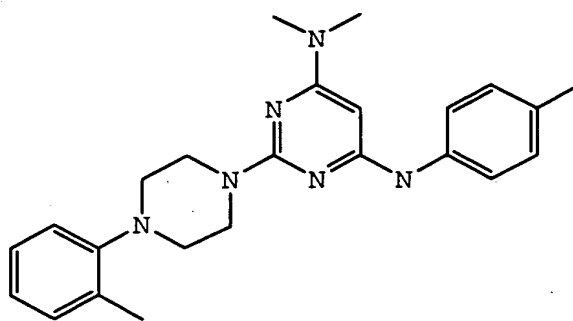


53. The method of claim 43, wherein Y is

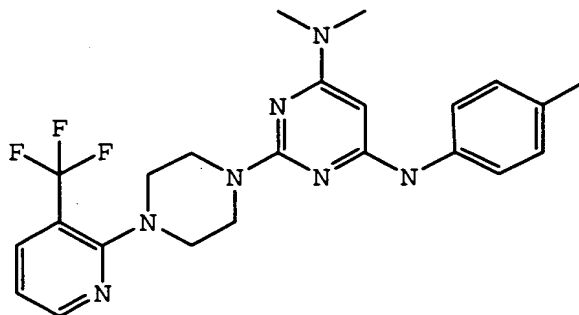


5 54. The method of claim 53, wherein  $U$  is  $NR_{16}$ .

55. The method of claim 54, wherein the compound is

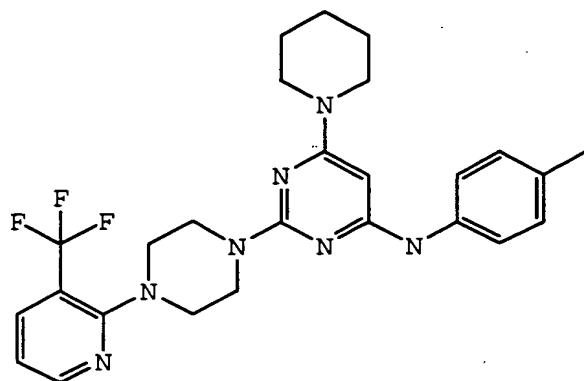


; or



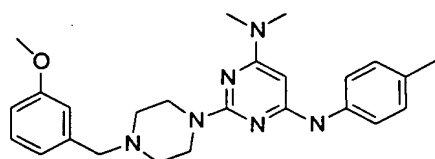


56. The method of claim 50, wherein the compound is

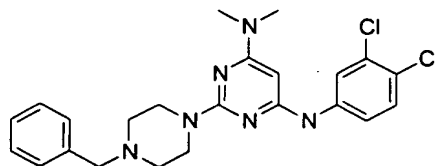


57. The method of claim 54, wherein the compound is selected from the group consisting of:

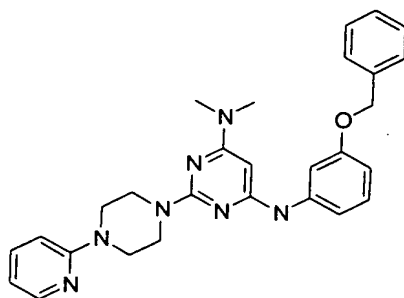
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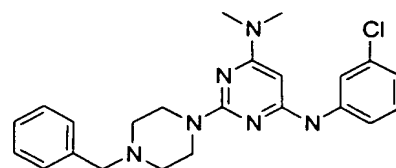
;



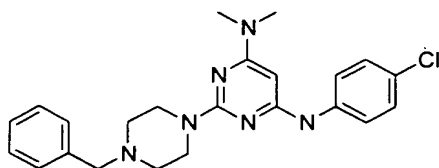
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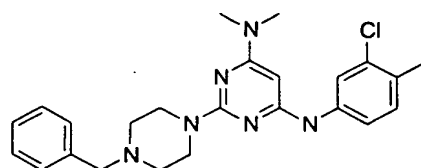
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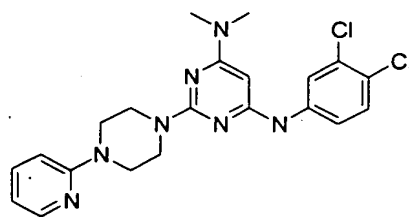
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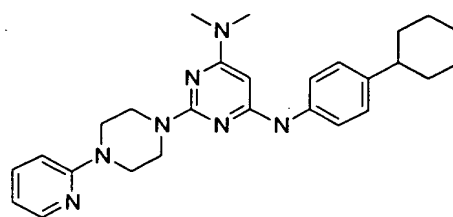
;



;

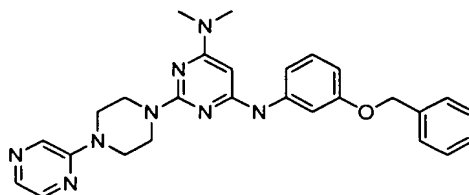
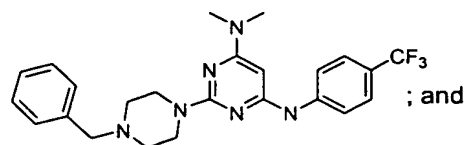
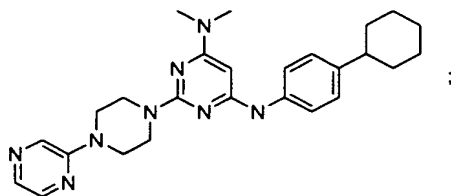
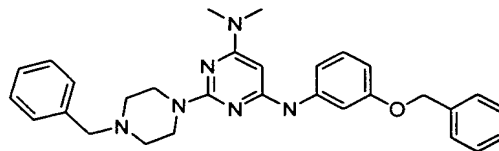
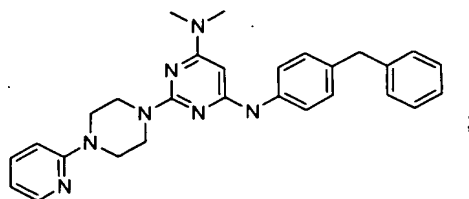
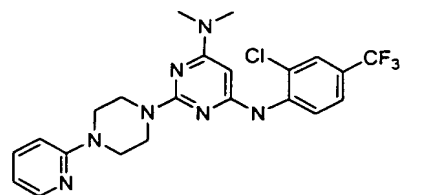
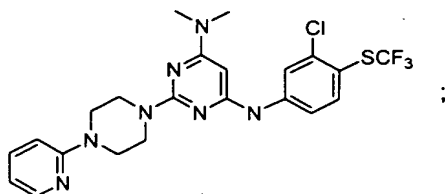
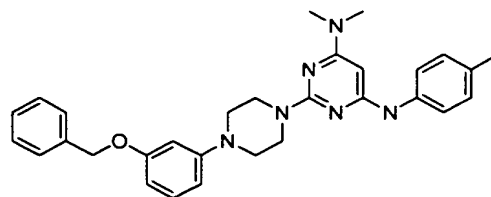
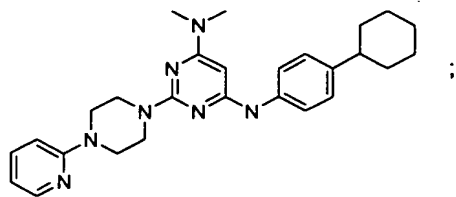


; and



10

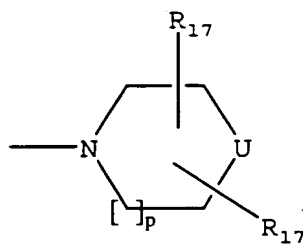
58. The method of claim 54, wherein the compound is selected from the group consisting of:



5

59. The method of claim 34, wherein X is  $N(CH_3)_2$ .

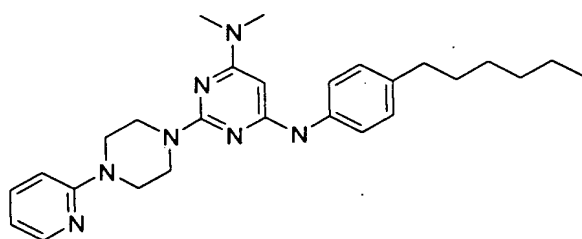
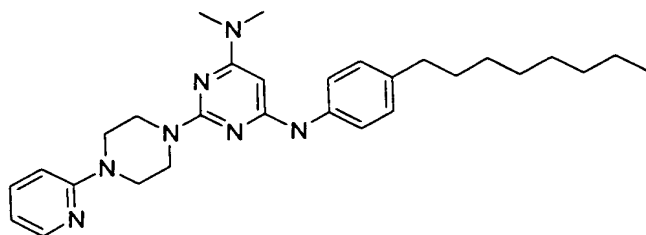
60. The method of claim 59, wherein Y is



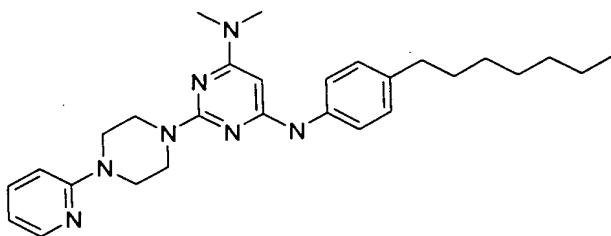
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61. The method of claim 60, wherein  $R_{13}$  is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained alkyl.

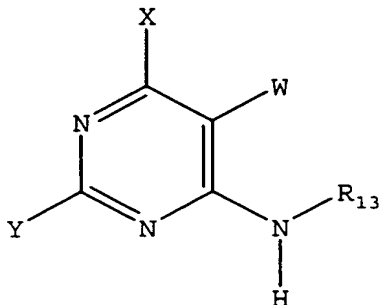
62. The method of claim 61, wherein the compound is selected from a group consisting of:



; and

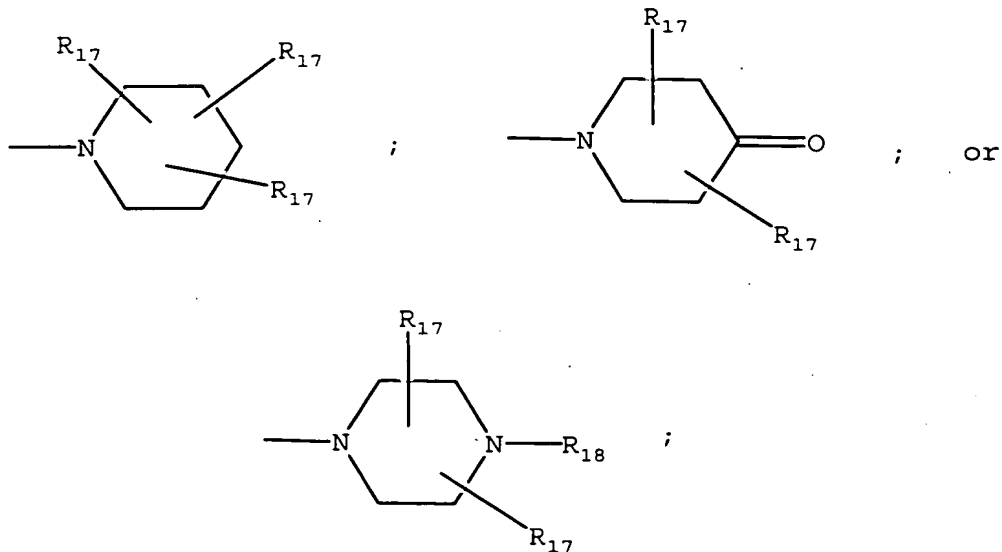


63. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



- 5 wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



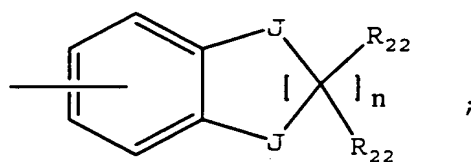
- 10 wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $R_{13}$  is a bicyclic alkyl ring system, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl, aryl, aryl( $C_1$ - $C_6$ )alkyl,  $Q_1$  or  $Q_2$ ;

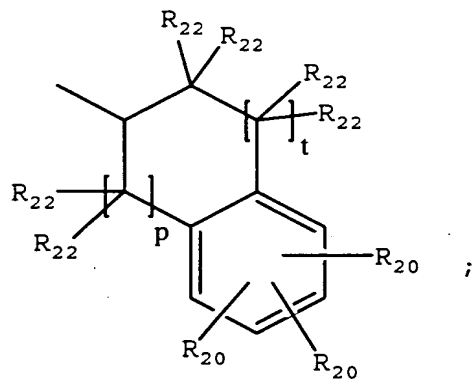
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wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

10 wherein  $Q_1$  is

wherein  $Q_2$  is

15

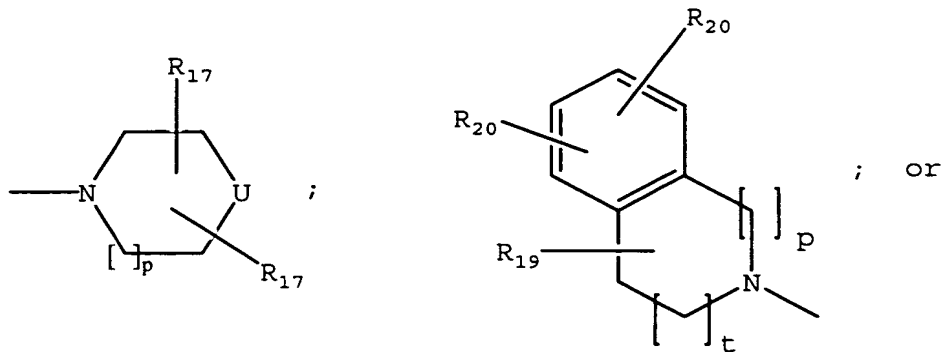


wherein each J is independently O, S,  $C(R_{22})_2$  or  $NR_4$ ;

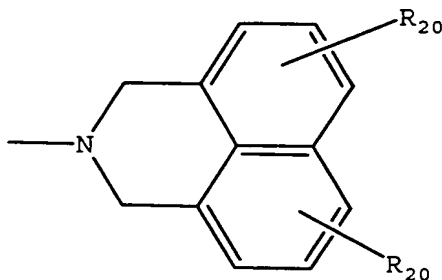
20 wherein  $R_4$  is H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$

cycloalkenyl or aryl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5



wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  
 10  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  
 $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl,  $(\text{C}(\text{R}_{19})_2)_m\text{N}(\text{R}_{16})_2$  or  
 $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

15

wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl,  
 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight  
 20 chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl, -



$(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

wherein each  $R_{17}$  is independently H;  $-\text{OR}_{21}$ ,  $-\text{OCOR}_{21}$ ,  $-\text{COR}_{21}$ ,  
 $-\text{NCOR}_{21}$ ,  $-\text{N}(\text{R}_{21})_2$ ,  $-\text{CON}(\text{R}_{21})_2$ ,  $-\text{COOR}_{21}$ , straight chained or  
 5 branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$   
 monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$   
 polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$   
 alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$   
 cycloalkenyl,  $-(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

10

wherein  $R_{18}$  is straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $-(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained  
 15 or branched  $\text{C}_1\text{-C}_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or  
 branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$   
 20  $\text{C}_7$  cycloalkyl or  $\text{C}_5\text{-C}_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  
 $-\text{NO}_2$ ;  $-\text{N}_3$ ;  $-\text{CN}$ ;  $-\text{OR}_{21}$ ,  $-\text{OCOR}_{21}$ ,  $-\text{COR}_{21}$ ,  $-\text{NCOR}_{21}$ ,  $-\text{N}(\text{R}_{21})_2$ ,  $-\text{CON}(\text{R}_{21})_2$ , or  $-\text{COOR}_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups  
 present on adjacent carbon atoms can join together to  
 form a methylenedioxy group;

25

wherein each  $R_{21}$  is independently -H; straight chained or  
 branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$   
 cycloalkyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl, aryl, or aryl( $\text{C}_1\text{-C}_6$ )alkyl;  
 30  $\text{C}_6$ )alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $\text{C}_1\text{-C}_4$

straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

5 wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

10

wherein t is 1 or 2;

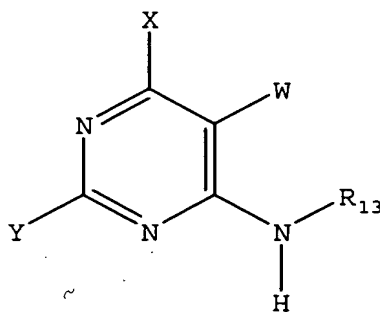
wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15 wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

a pharmaceutically acceptable salt thereof.

20

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

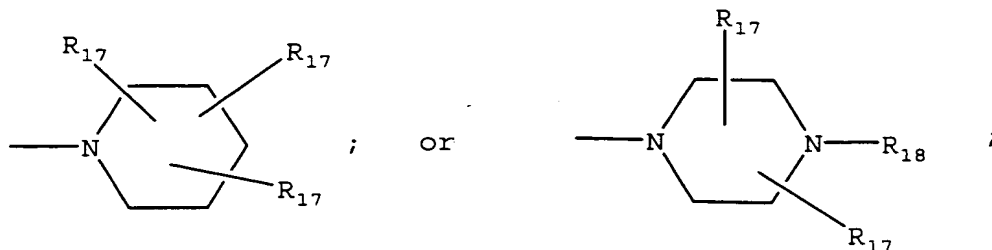


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wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl,

propyl, methoxy or ethoxy;

wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



5 wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

10

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;

15



5

10

15

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

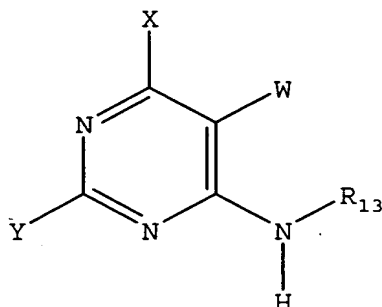
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wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

10 a pharmaceutically acceptable salt thereof.

65. A pharmaceutical composition comprising a  
pharmaceutically acceptable carrier and a compound  
15 having the structure:

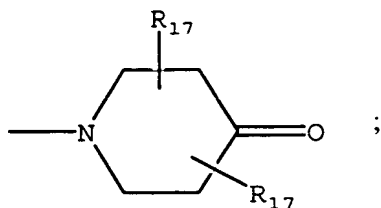


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wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is N(CH<sub>3</sub>)<sub>2</sub> or

25

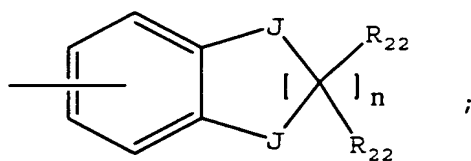


wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

5

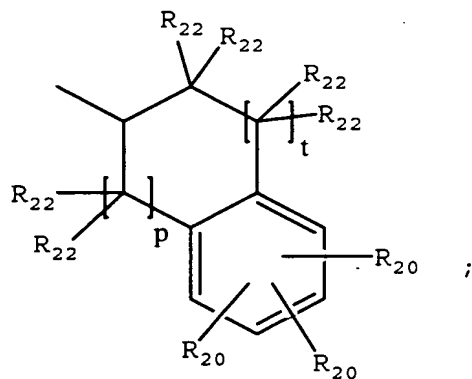
wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

10 wherein  $Q_1$  is



wherein  $Q_2$  is

15

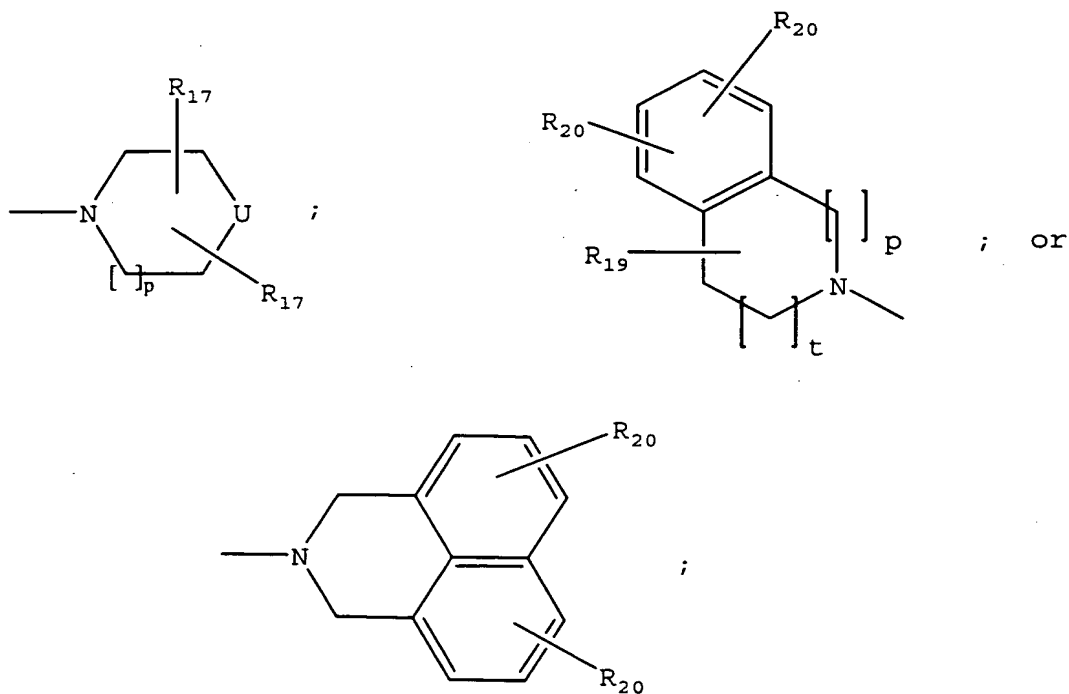


wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

5

wherein Y is  $NR_{14}R_{15}$ ;



10 wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ -CH<sub>3</sub>,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

15

wherein U is O, - $NR_{16}$ , S,  $C(R_{17})_2$ , or - $NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;



wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl,  
 5 straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  
 10  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$   
 15 cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

20 wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 25 straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to  
 30 form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or

branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5

wherein each R<sub>22</sub> is independently H, F, Cl or C<sub>1</sub>-C<sub>4</sub> straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

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wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

15

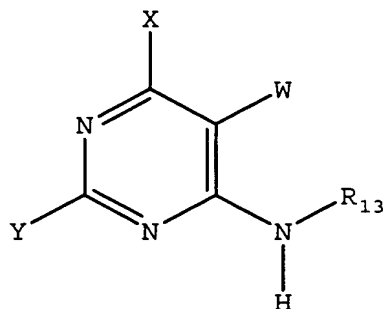
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

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66. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



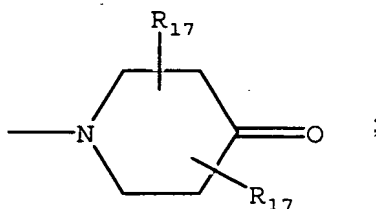
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wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

10

wherein X is  $N(CH_3)_2$  or



15

wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20

wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

25

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -

$(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

wherein each  $R_{17}$  is independently H;  $-\text{OR}_{21}$ ,  $-\text{OCOR}_{21}$ ,  $-\text{COR}_{21}$ ,  
 $-\text{NCOR}_{21}$ ,  $-\text{N}(\text{R}_{21})_2$ ,  $-\text{CON}(\text{R}_{21})_2$ ,  $-\text{COOR}_{21}$ , straight chained or  
 5 branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$   
 monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$   
 polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$   
 alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$   
 cycloalkenyl,  $-(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ ;

10

wherein each  $R_{19}$  is independently H, or straight chained  
 or branched  $\text{C}_1\text{-C}_6$  alkyl;

wherein each  $R_{21}$  is independently -H; straight chained or  
 15 branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$   
 cycloalkyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl, aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

20 wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein  $q$  is an integer from 2 to 4 inclusive; or

25

a pharmaceutically acceptable salt thereof.

67. The pharmaceutical composition of claim 63, 64, 65  
 or 66, wherein the compound is enantiomerically and  
 30 diasteriomERICALLY pure.

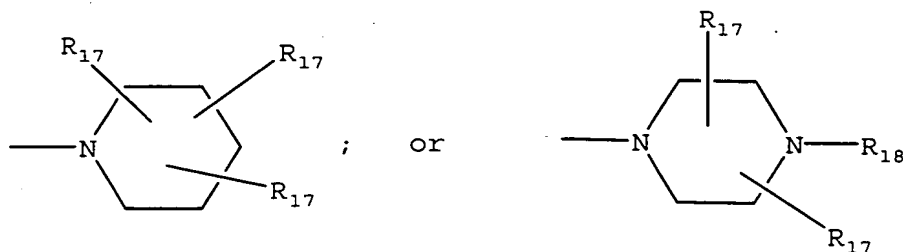
68. The pharmaceutical composition of claim 63, 64, 65

or 66, wherein the compound is enantiomerically or diasteriomERICALLY pure.

69. The pharmaceutical composition of claim 63, 64, 65  
5 or 66,, wherein the compound can be administered orally.

70. The pharmaceutical composition of claim 63, wherein  
X is:

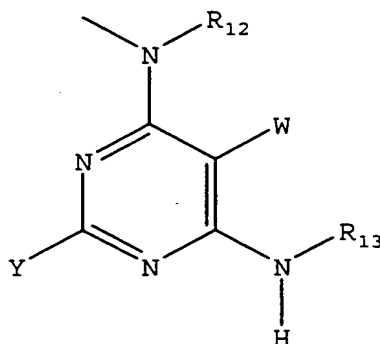
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20 71. The pharmaceutical composition of claim 63, wherein  
X is  $NR_{11}R_{12}$  and  $R_{11}$  is H or straight chained or  
branched  $C_1$ - $C_7$  alkyl.

72. The pharmaceutical composition of claim 71, wherein the compound has the structure:

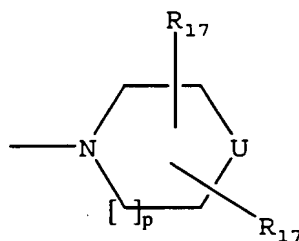


- 5 73. The pharmaceutical composition of claim 70, wherein  $R_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.
- 10 74. The pharmaceutical composition of claim 72, wherein  $R_{13}$  is a bicyclic alkyl ring system, cyclohexyl or aryl.
- 15 75. The pharmaceutical composition of claim 73, wherein  $R_{14}$  is H, straight chained or branched  $C_1-C_6$  alkyl or  $(CH_2)_q-O-(CH_2)_m-CH_3$ .
- 20 76. The pharmaceutical composition of claim 74, wherein  $R_{14}$  is H, straight chained or branched  $C_1-C_6$  alkyl or  $(CH_2)_q-O-(CH_2)_m-CH_3$ .

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77. The pharmaceutical composition of claim 73, wherein Y is



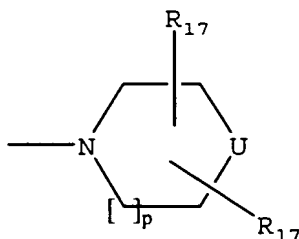
- 5 78. The pharmaceutical composition of claim 77, wherein U is  $\text{NR}_{16}$ .

- 79 The pharmaceutical composition of claim 78, wherein  $\text{R}_{16}$  is  $(\text{CH}_2)_m\text{-Z}$ .

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80. The pharmaceutical composition of claim 79, wherein Z is aryl or heteroaryl.

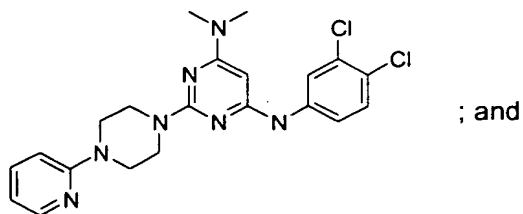
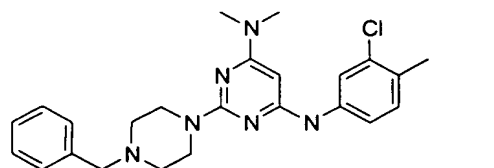
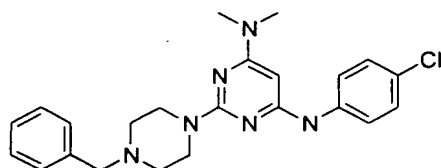
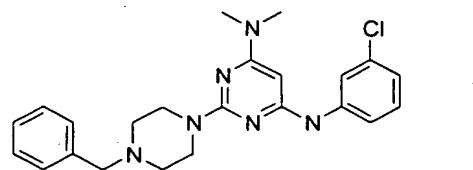
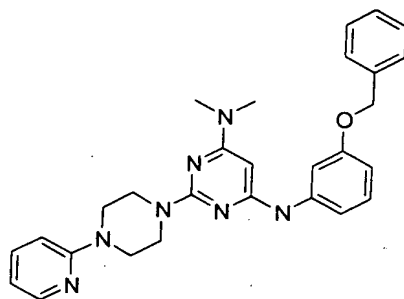
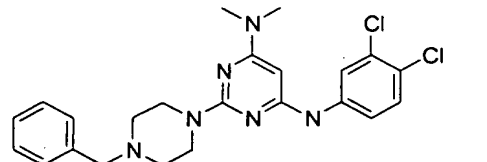
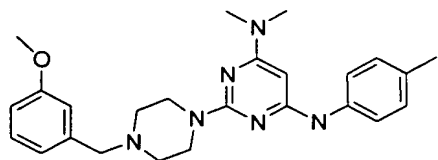
- 15 81. The pharmaceutical composition of claim 74, wherein Y is



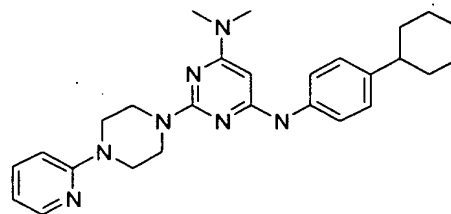
- 20 82. The pharmaceutical composition of claim 81, wherein U is  $\text{NR}_{16}$ .

83. The pharmaceutical composition of claim 82, wherein the compound is selected from the group consisting of:

5



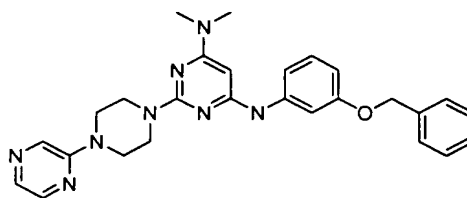
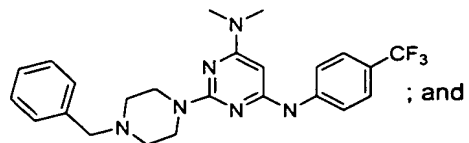
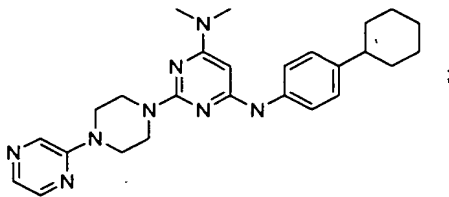
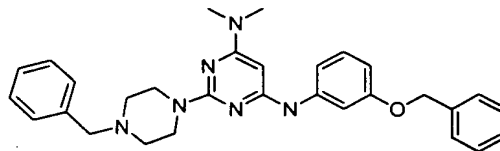
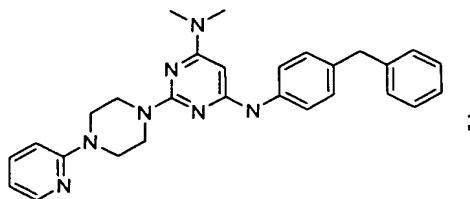
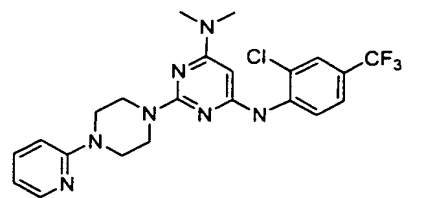
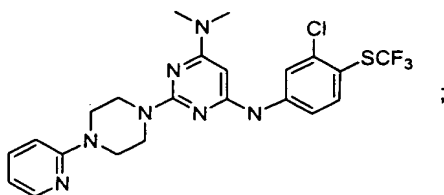
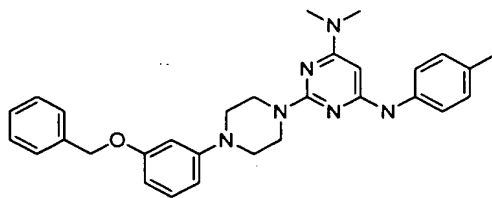
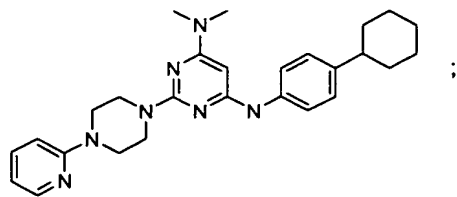
; and



10

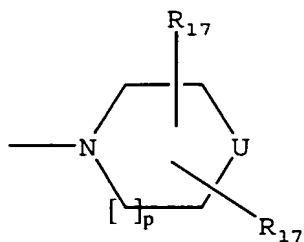


84. The pharmaceutical composition of claim 82, wherein the compound is selected from the group consisting of:



85. The pharmaceutical composition of claim 65, wherein  
X is  $N(CH_3)_2$ .

86. The pharmaceutical composition of claim 85, wherein  
5 Y is



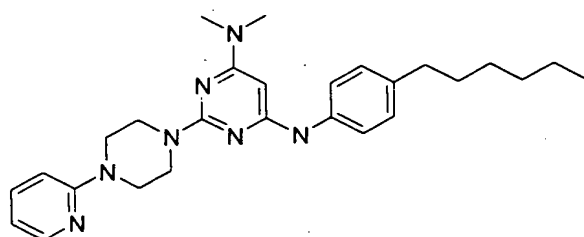
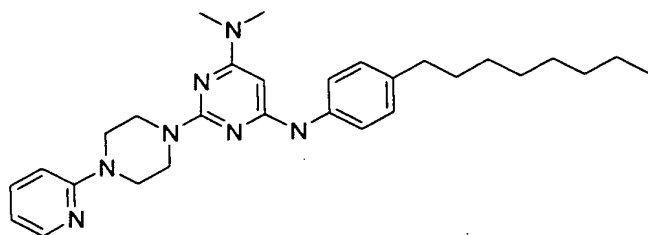
10 87. The pharmaceutical composition of claim 86, wherein  $R_{13}$   
is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained  
alkyl.

15

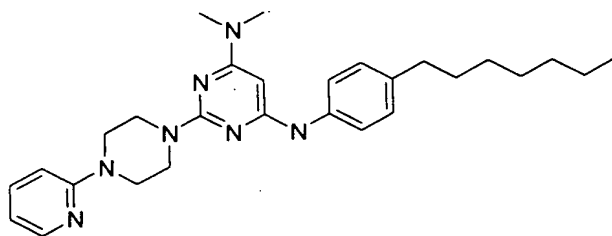
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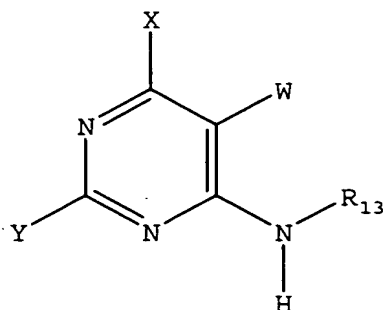
88. The pharmaceutical composition of claim 87, wherein the compound is selected from a group consisting of:



; and



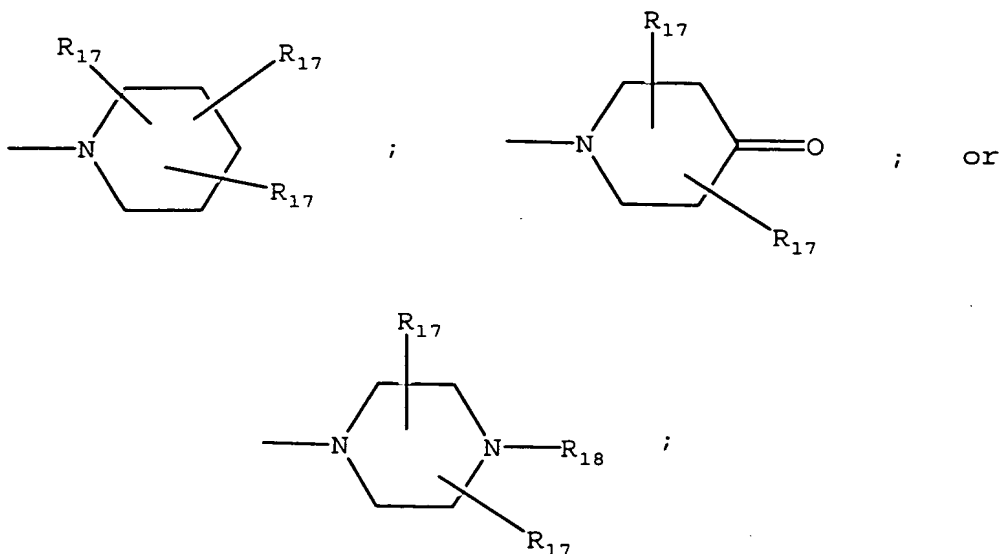
89. A compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

5

wherein X is;  $\text{NR}_{11}\text{R}_{12}$ ;



wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl, or aryl  $(\text{C}_1\text{-C}_6)$  alkyl;

10

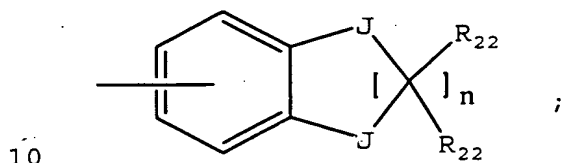
wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $-(\text{CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, adamantyl,

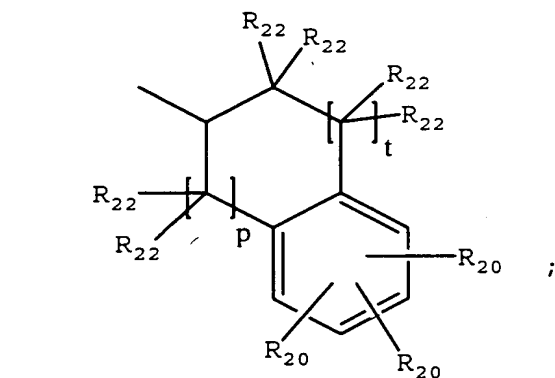
noradamantyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, heteroaryl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, Q<sub>1</sub> or Q<sub>2</sub>;

wherein aryl may be substituted with one or more C<sub>1</sub>-C<sub>10</sub>  
 5 straight chained or branched alkyl, aryl, heteroaryl, or  
 N(R<sub>19</sub>)-Z;

wherein Q<sub>1</sub> is



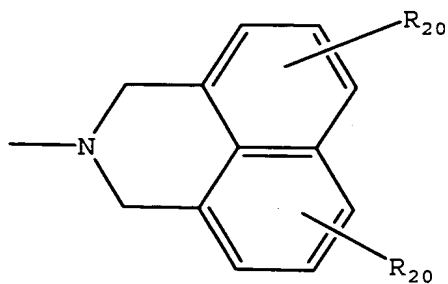
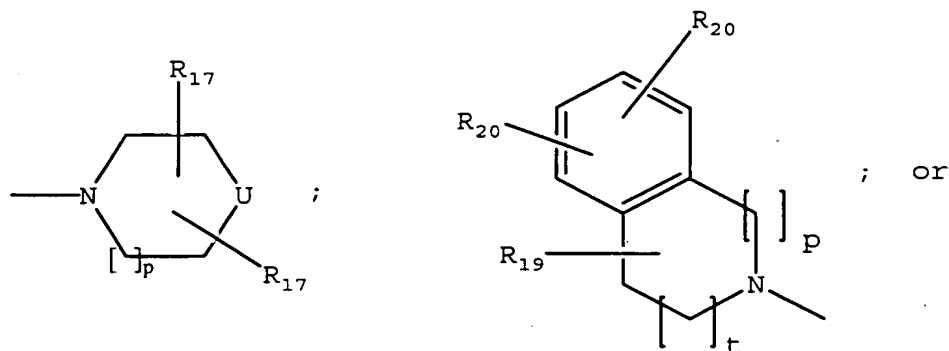
wherein Q<sub>2</sub> is



wherein each J is independently O, S, C(R<sub>22</sub>)<sub>2</sub> or NR<sub>4</sub>;

wherein R<sub>4</sub> is H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained or  
 20 branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub>  
 cycloalkenyl or aryl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

10 wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl,  $(\text{C}(\text{R}_{19})_2)_m\text{N}(\text{R}_{16})_2$  or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

15 wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_5\text{-C}_7$  cycloalkenyl,  $-(\text{CH}_2)_m\text{-Z}$ , or  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ;

20

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl, or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1$ - $C_4$  straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

5 wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

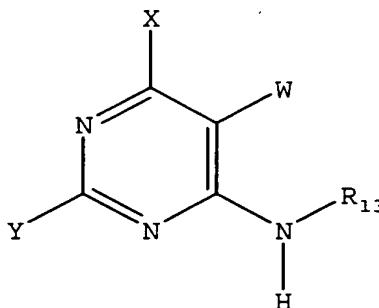
wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

90. A compound having the structure:

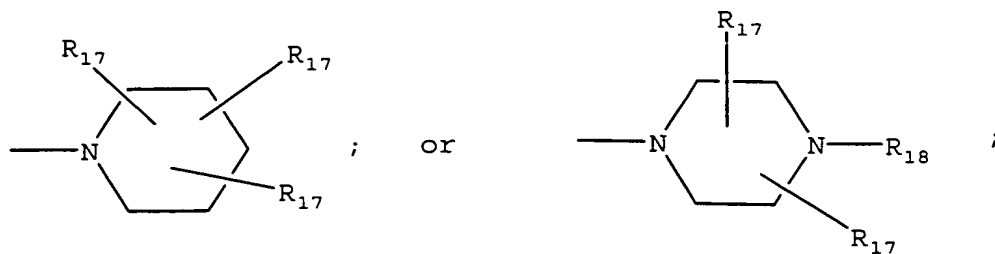
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wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;



wherein X is  $\text{NR}_{11}\text{R}_{12}$ ;



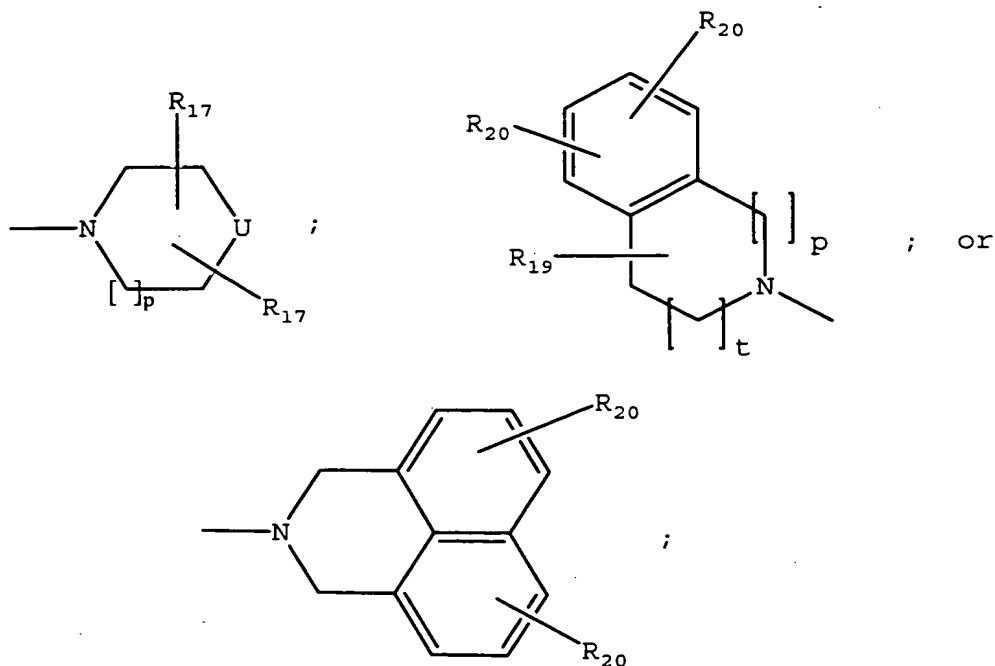
wherein  $\text{R}_{11}$  is H, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , aryl or aryl( $\text{C}_1\text{-C}_6$ )alkyl;

5

wherein  $\text{R}_{12}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ , or  $\text{-(CH}_2)_m\text{-Z}$ ;

wherein  $\text{R}_{13}$  is a bicyclic alkyl ring system, aryl or  
10 aryl( $\text{C}_1\text{-C}_6$ )alkyl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

5

wherein  $R_{15}$  is straight chained or branched  $C_3$ - $C_6$  alkyl,  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m$ -Z;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

10

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m$ -Z, or  $(CH_2)_q$ -O- $(CH_2)_m$ - $CH_3$ ;

15

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein  $R_{18}$  is straight chained or branched  $C_1$ - $C_6$  alkyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1$ - $C_6$  alkyl;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

5

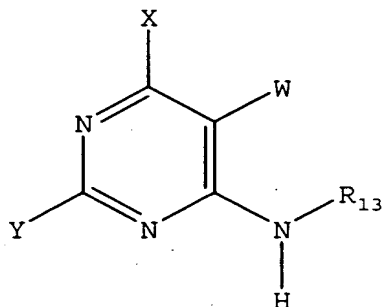
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

10 a pharmaceutically acceptable salt thereof.

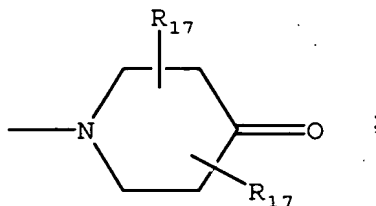
91. A compound having the structure:

15



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

20 wherein X is  $N(CH_3)_2$  or

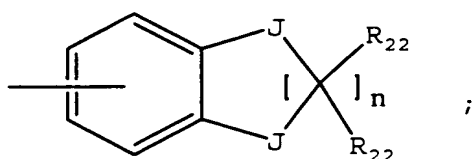


wherein  $R_{13}$  is an aryl, adamantyl, noradamantyl,  $C_3$ - $C_{10}$  cycloalkyl, heteroaryl,  $Q_1$  or  $Q_2$ ;

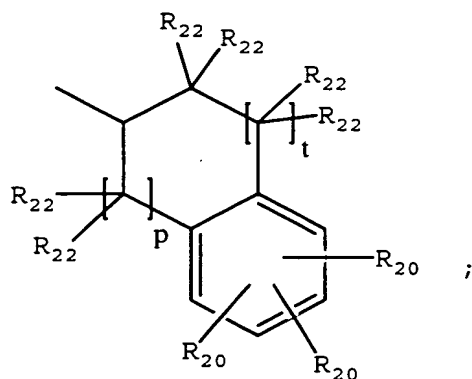
5 wherein aryl may be substituted with one or more  $C_1$ - $C_{10}$  straight chained or branched alkyl, aryl, heteroaryl, or  $N(R_{19})-Z$ ;

wherein  $Q_1$  is

10



wherein  $Q_2$  is

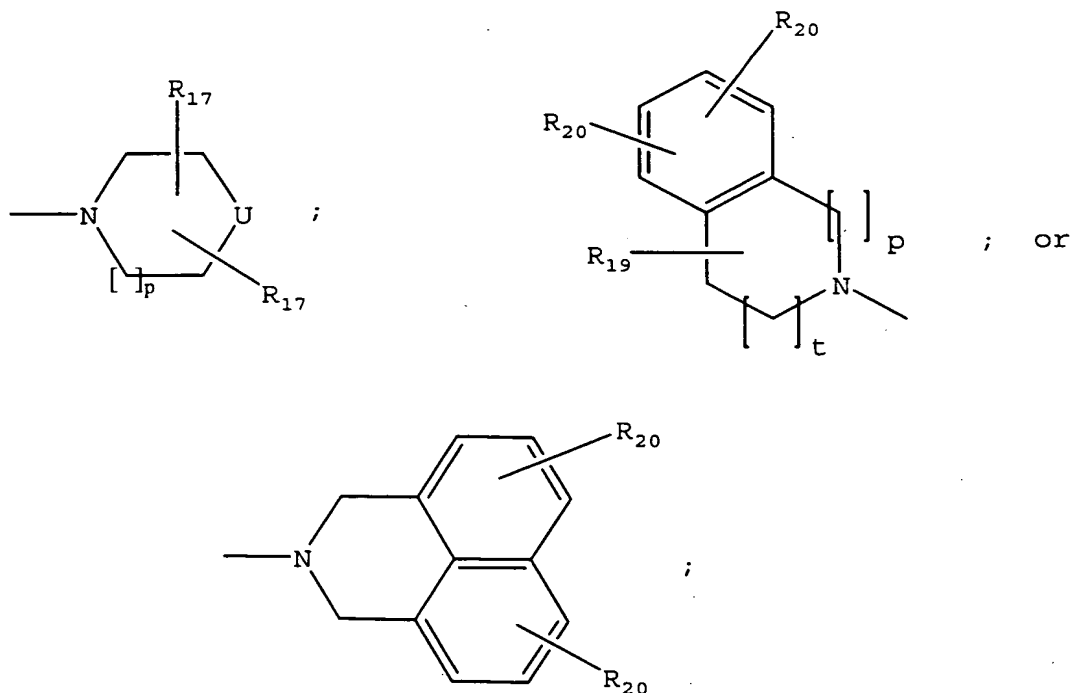


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wherein each  $J$  is independently  $O$ ,  $S$ ,  $C(R_{22})_2$  or  $NR_4$ ;

wherein  $R_4$  is  $-H$ ; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight  
 20 chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein Y is  $\text{NR}_{14}\text{R}_{15}$ ;



5

wherein  $\text{R}_{14}$  is H, straight chained or branched  $\text{C}_1\text{-C}_6$  alkyl,  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein  $\text{R}_{15}$  is straight chained or branched  $\text{C}_3\text{-C}_6$  alkyl,  
 10  $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$ ,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$ ;

wherein U is O,  $\text{-NR}_{16}$ , S,  $\text{C}(\text{R}_{17})_2$ , or  $\text{-NSO}_2\text{R}_{16}$ ;

wherein Z is  $\text{C}_3\text{-C}_{10}$  cycloalkyl, aryl, or heteroaryl;

15

wherein  $\text{R}_{16}$  is straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl,  
 straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl,

straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

- 5 wherein each R<sub>17</sub> is independently H; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, -COOR<sub>21</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein R<sub>18</sub> is straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

15

wherein each R<sub>19</sub> is independently H, or straight chained or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

- 20 wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

- 30 wherein each R<sub>21</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

wherein each  $R_{22}$  is independently H, F, Cl or  $C_1-C_4$  straight chained or branched alkyl;

5 wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

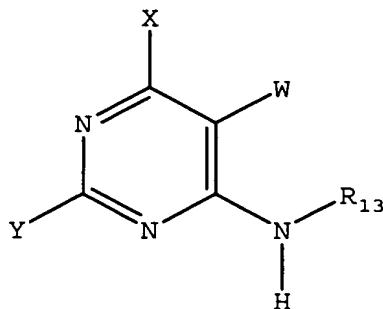
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wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

15 a pharmaceutically acceptable salt thereof.

92. A compound having the structure:



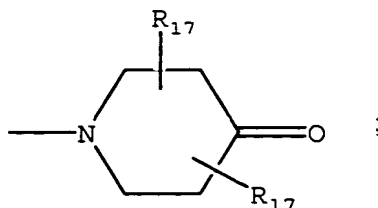
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wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is  $N(CH_3)_2$  or

25





wherein  $R_{13}$  is a bicyclic alkyl ring system, aryl or aryl( $C_1$ - $C_6$ )alkyl;

5

wherein Y is  $NR_{14}R_{15}$ ;

wherein  $R_{14}$  is H, straight chained or branched  $C_1$ - $C_6$  alkyl,  $(CH_2)_q-O-(CH_2)_m-CH_3$ ,  $C_3$ - $C_6$  cycloalkyl, or  $(C(R_{19})_2)_m-Z$ ;

10

wherein  $R_{15}$  is  $(C(R_{19})_2)_m-N(R_{16})_2$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl, aryl, or heteroaryl;

15 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl, -  
20  $(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{17}$  is independently H;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ ,  $-COOR_{21}$ , straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

25

wherein each  $R_{19}$  is independently H, or straight chained or branched  $C_1-C_6$  alkyl;

wherein each  $R_{21}$  is independently -H; straight chained or  
 5 branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl;  
 straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

10 wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein  $q$  is an integer from 2 to 4 inclusive; or

15

a pharmaceutically acceptable salt thereof.

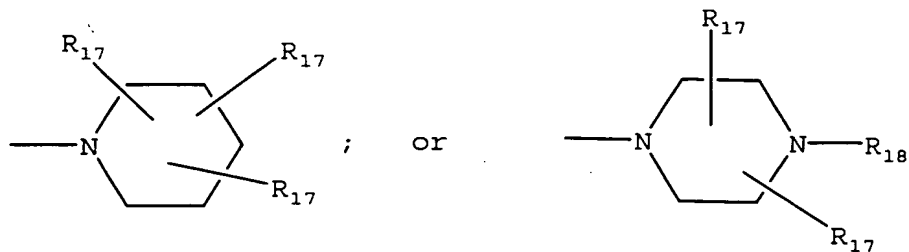
93. An enantiomerically and diastereomerically pure compound of claim 89, 90, 91, or 92.

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94. An enantiomerically or diastereomerically pure compound of claim 89, 90, 91, or 92.

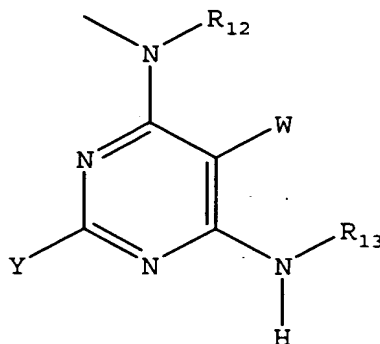
95. The compound of claim 89, wherein X is:

25



96. The compound of claim 88, wherein X is  $\text{NR}_{11}\text{R}_{12}$  and  $\text{R}_{11}$  is H or straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl.

5 97. The compound of claim 96, wherein the compound has the structure:



98. The compound of claim 95, wherein  $\text{R}_{13}$  is a bicyclic  
10 alkyl ring system, cyclohexyl or aryl.

99. The compound of claim 97, wherein  $\text{R}_{13}$  is a bicyclic  
alkyl ring system, cyclohexyl or aryl.

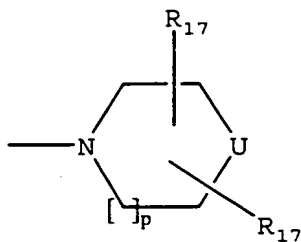
15 100. The compound of claim 98, wherein  $\text{R}_{14}$  is H, straight  
chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

101. The compound of claim 99, wherein  $\text{R}_{14}$  is H, straight  
chained or branched  $\text{C}_1\text{-C}_6$  alkyl or  $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$ .

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25

102. The compound of claim 98, wherein Y is



103. The compound of claim 102, wherein U is  $\text{NR}_{16}$ .

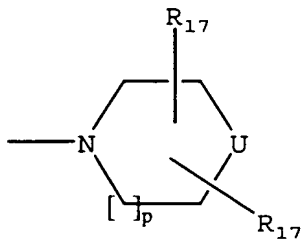
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104. The compound of claim 103, wherein  $\text{R}_{16}$  is  $(\text{CH}_2)_m\text{-Z}$ .

105. The compound of claim 104, wherein Z is aryl or heteroaryl.

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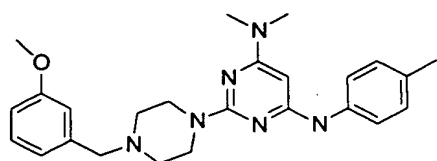
106. The compound of claim 99, wherein Y is



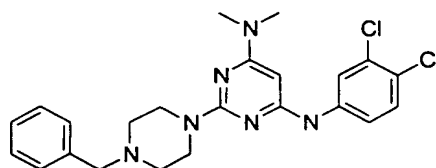
15 107. The compound of claim 106, wherein U is  $\text{NR}_{16}$ .

108. The compound of claim 107, wherein the compound is selected from the group consisting of:

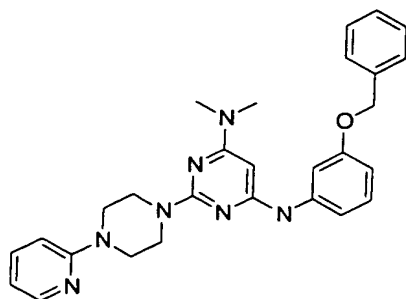
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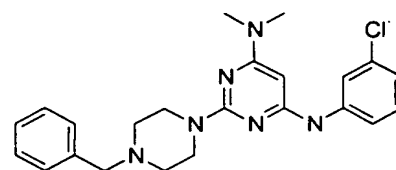
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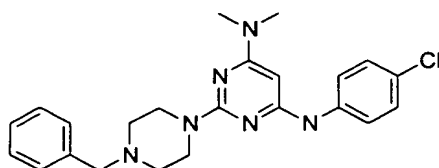
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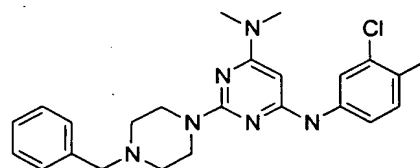
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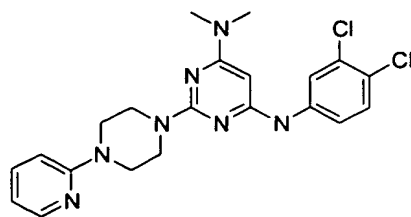
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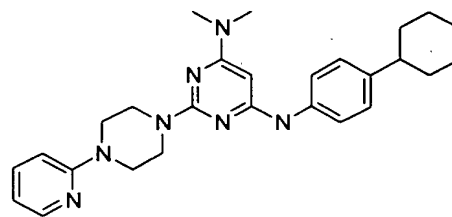
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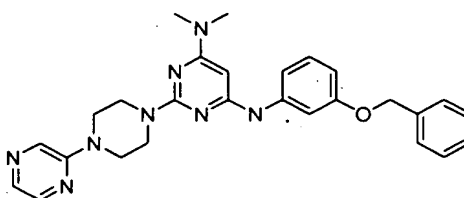
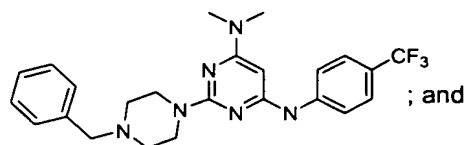
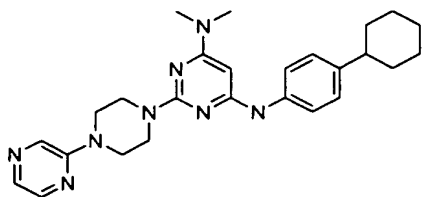
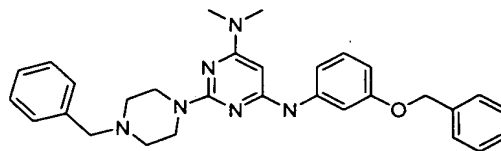
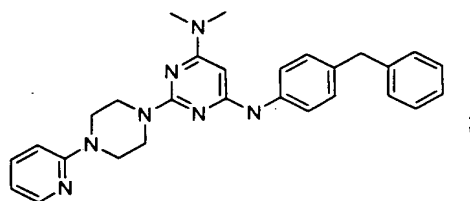
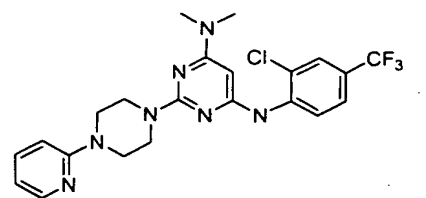
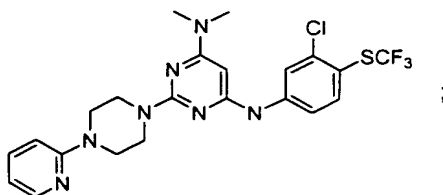
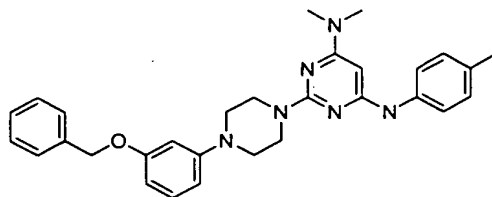
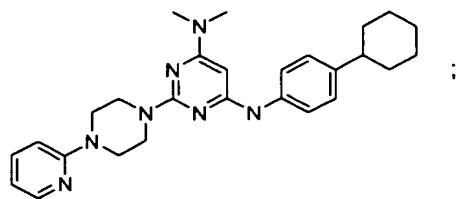
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; and

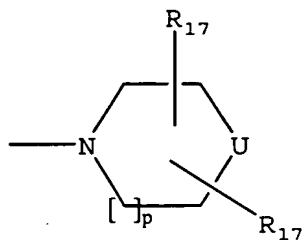


109. The compound of claim 107, wherein the compound is selected from the group consisting of:



110. The compound of claim 89, wherein X is  $N(CH_3)_2$ .

111. The compound of claim 110, wherein Y is



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111. The compound of claim 110, wherein  $R_{13}$  is an aryl substituted with a  $C_1$ - $C_{10}$  straight chained alkyl.

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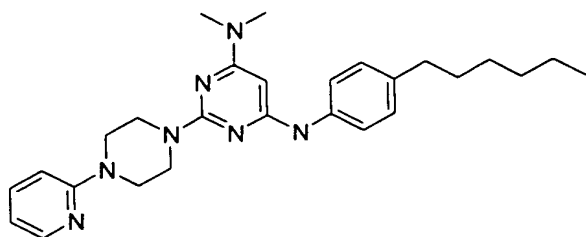
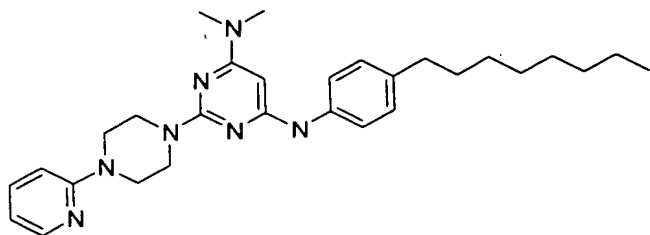
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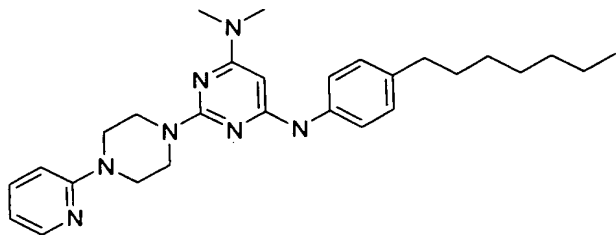
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112. The compound of claim 111, wherein the compound is selected from a group consisting of:

5



; and



10 113. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 89, 90, 91, or 92 and a pharmaceutically acceptable carrier.

15 114. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 89, 90, 91, or 92 and a pharmaceutically acceptable carrier.



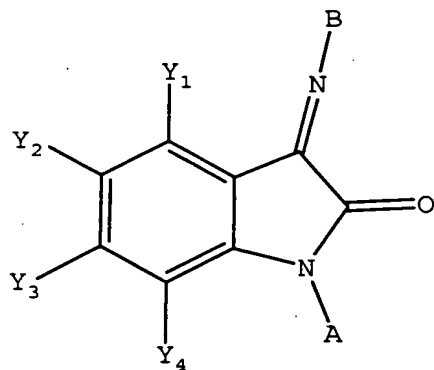
115. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 89, 90, 91, or 92 and a pharmaceutically acceptable carrier.

116. A method of treating a subject suffering from depression which comprises administering to the subject an amount of the compound of claim 89, 90, 91, or 92 effective to treat the subject's depression.

117. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of the compound of claim 89, 90, 91, or 92 effective to treat the subject's anxiety.

118. A method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of the compound of claim 89, 90, 91, or 92 effective to treat the subject's depression and anxiety.

119. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 10 H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 15  $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

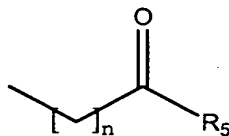
wherein each  $R_4$  is independently -H; straight chained  
 20 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

25 wherein A is  $A'$ ,  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or

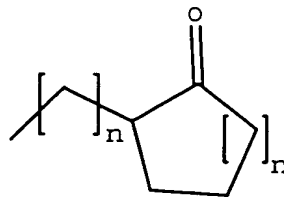
branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl, heteroaryl( $C_1$ - $C_6$ )alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or  $(CHR_{17})-(CHR_{17})_n-Z$ ;

5

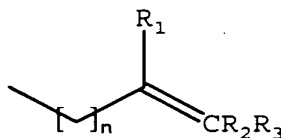
wherein  $A'$  is



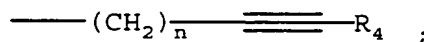
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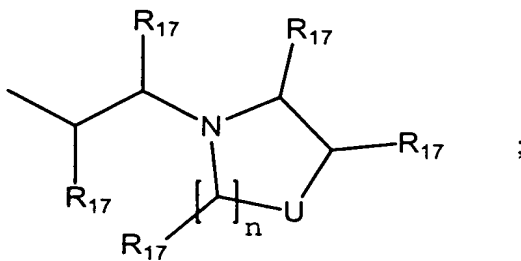
; or



;

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wherein  $Q_3$  is

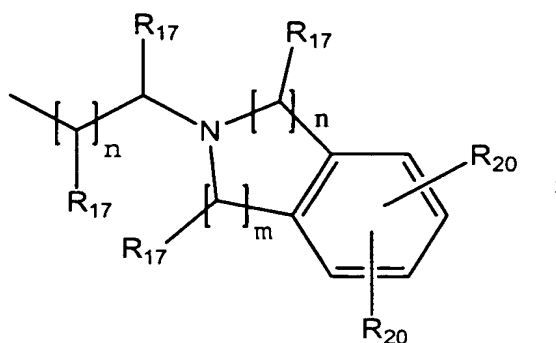


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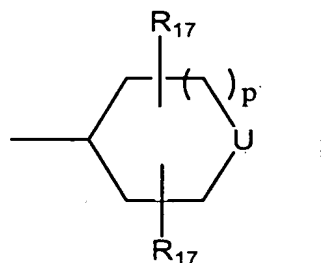
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wherein  $Q_4$  is



wherein  $Q_5$  is



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wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

10

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, - $OR_6$ , aryl or heteroaryl;

15

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, - $N(R_4)_2$ , - $OR_6$  or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

20

wherein each  $R_{17}$  is independently H; straight chained

or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each  $p$  is an integer from 0 to 2 inclusive;

wherein  $U$  is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein  $Z$  is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,

C<sub>4</sub>-C<sub>7</sub> cyclic thioether, aryl, or heteroaryl;

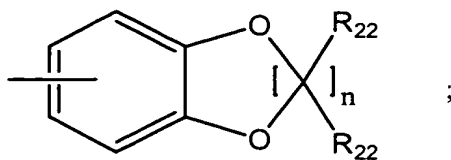
wherein R<sub>16</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

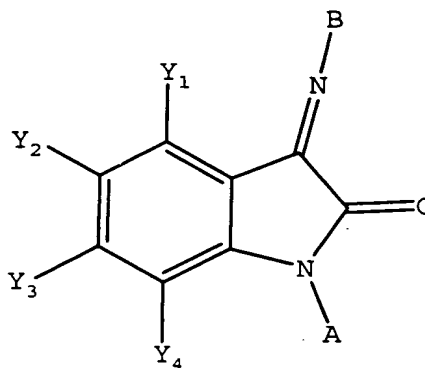
wherein Q<sub>6</sub> is



wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

120. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

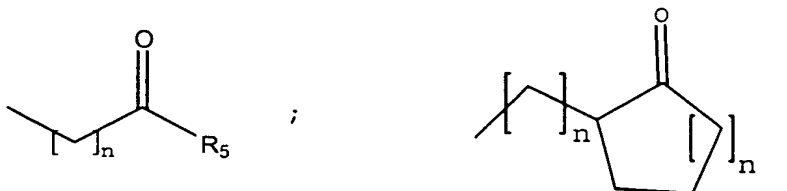


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

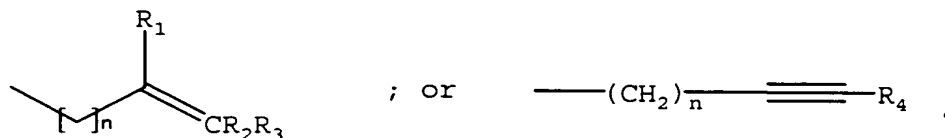
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5



wherein A' is



10

wherein R<sub>1</sub> and R<sub>2</sub> are each independently H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, or -CN;

15

wherein R<sub>3</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub> aryl or heteroaryl;

20

wherein R<sub>5</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>6</sub> or aryl;

wherein R<sub>6</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub>



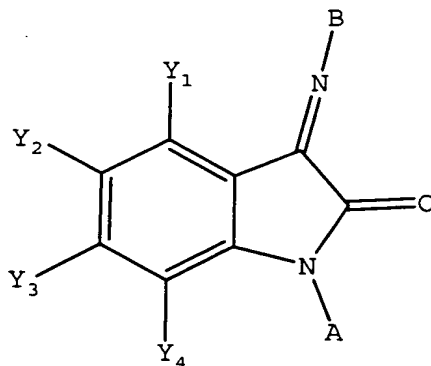
alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however,  
if B is aryl or heteroaryl the carbon atom or carbon  
atoms ortho to the nitrogen atom of the imine bond  
may only be substituted with one or more of the  
following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

121. A method of treating a subject suffering from  
depression which comprises administering to the  
subject an amount of compound effective to treat the  
subject's depression wherein the compound has the  
structure:



wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, and Y<sub>4</sub> is independently -  
H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
monofluoroalkyl or polyfluoroalkyl; straight chained  
or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub>  
cycloalkyl, or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -

I;  $-\text{NO}_2$ ;  $-\text{N}_3$ ;  $-\text{CN}$ ;  $-\text{OR}_4$ ,  $-\text{SR}_4$ ,  $-\text{OCOR}_4$ ,  $-\text{COR}_4$ ,  $-\text{NCOR}_4$ ,  $-\text{N}(\text{R}_4)_2$ ,  $-\text{CON}(\text{R}_4)_2$ , or  $-\text{COOR}_4$ ; aryl or heteroaryl; or any two of  $\text{Y}_1$ ,  $\text{Y}_2$ ,  $\text{Y}_3$  and  $\text{Y}_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

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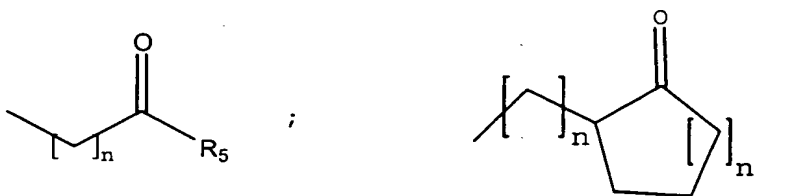
wherein each  $\text{R}_4$  is independently  $-\text{H}$ ; straight chained or branched  $\text{C}_1$ - $\text{C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $\text{C}_2$ - $\text{C}_7$  alkenyl or alkynyl;  $\text{C}_3$ - $\text{C}_7$  cycloalkyl,  $\text{C}_5$ - $\text{C}_7$  cycloalkenyl, aryl or aryl( $\text{C}_1$ - $\text{C}_6$ )alkyl;

10

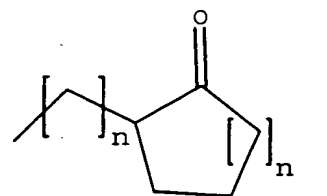
wherein A is A', straight chained or branched  $\text{C}_1$ - $\text{C}_7$  alkyl, aryl, heteroaryl, aryl( $\text{C}_1$ - $\text{C}_6$ )alkyl or heteroaryl( $\text{C}_1$ - $\text{C}_6$ )alkyl;

15

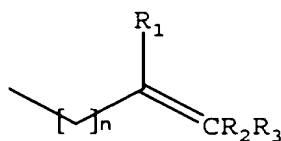
wherein A' is



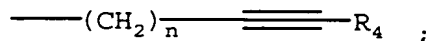
;



;



; or



;

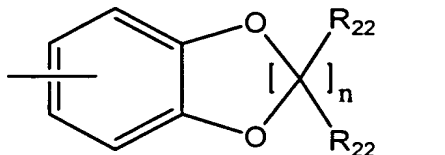
20

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or

heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is

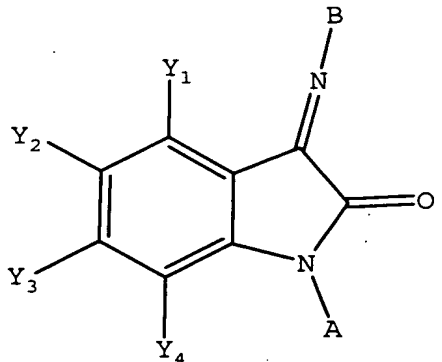


wherein n is an integer from 1 to 4 inclusive;

wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof.

122. A method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

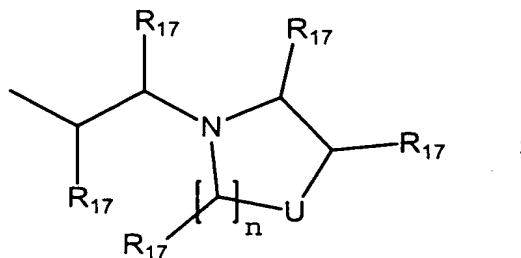


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 5 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -  
 N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
 10 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

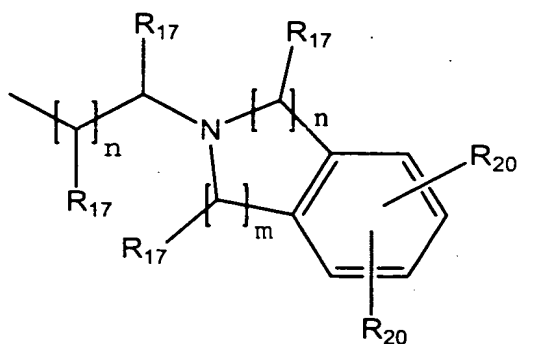
wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $Q_3$ ,  $Q_4$ ,  $Q_5$ , aryl substituted with an  
 aryl or heteroaryl, heteroaryl substituted with an  
 20 aryl or heteroaryl, or (CHR<sub>17</sub>) - (CHR<sub>17</sub>)<sub>n</sub>-Z;

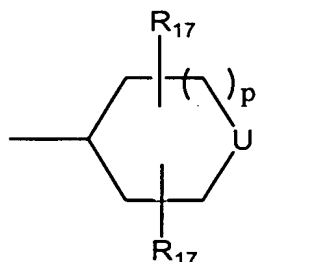
wherein  $Q_3$  is



25 wherein  $Q_4$  is



wherein  $Q_5$  is



5

wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

15

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_{21}$ , - $OCOR_{21}$ , - $COR_{21}$ , - $NCOR_{21}$ , - $N(R_{21})_2$ , - $CON(R_{21})_2$ , or - $COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a

20

methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight  
 chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 5 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F,  
 10 Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

15

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

20 wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  
 $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

25 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$   
 alkyl, straight chained or branched  $C_1$ - $C_7$   
 monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$   
 polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$   
 alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  
 30  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein B is aryl, or heteroaryl; provided however,

if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

10 123. The method of claim 119, 120, 121, or 122, wherein the compound is enantiomerically and diastereomerically pure.

15 124. The method of claim 119, 120, 121, or 122, wherein the compound is enantiomerically or diastereomerically pure.

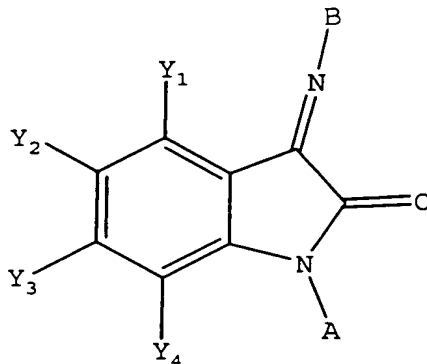
20 125. The method of claim 119, 120, 121, or 122, wherein the compound is a pure Z imine isomer or a pure Z alkene isomer.

25 126. The method of claim 119, 120, 121, or 122, wherein the compound is a pure E imine isomer or a pure E alkene isomer.

127. The method of claim 119, 120, 121, or 122, wherein the compound is administered orally.

30

128. The method of claim 119 or 120, wherein the compound has the structure:



5

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -F, -Cl, -Br, -I,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

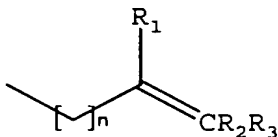
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wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

15

wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl; and

wherein  $A'$  is



20

129. The method of claim 119, 120 or 122, wherein B is heteroaryl.



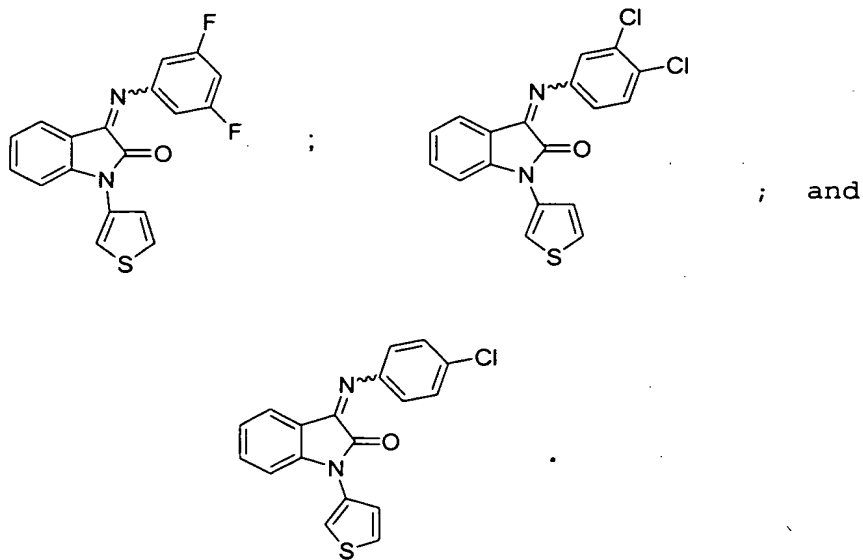
130. The method of claim 119 or 120, wherein B is aryl.

131. The method of claim 130, wherein B is phenyl and the  
 5 phenyl is optionally substituted with one or more of  
 the following: -F, -Cl, -Br, -CF<sub>3</sub>, straight chained  
 or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>,  
 -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

10 132. The method of claim 131, wherein A is aryl.

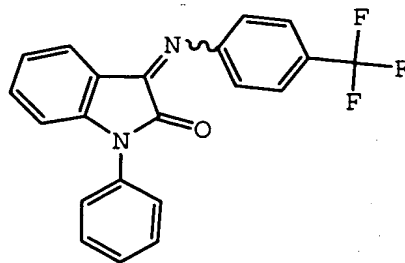
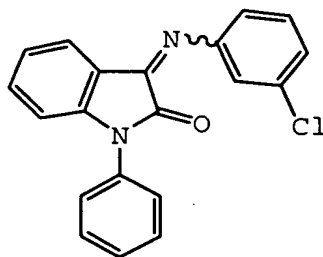
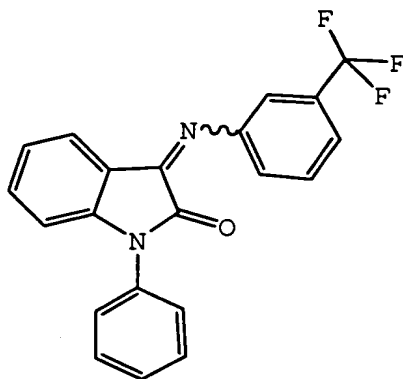
133. The method of claim 131, wherein A is heteroaryl.

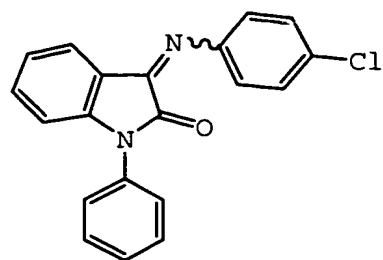
134. The method of claim 133, wherein the compound is  
 15 selected from the group consisting of:



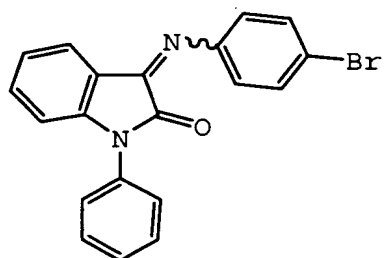
135. The method of claim 132, wherein the compound is selected from the group consisting of:

5

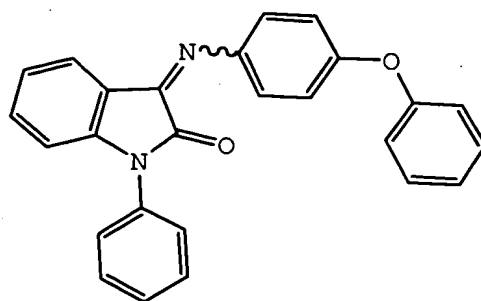




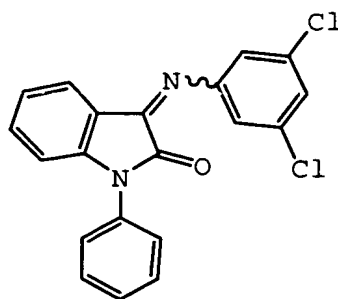
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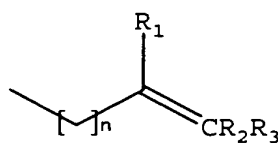
;



; and

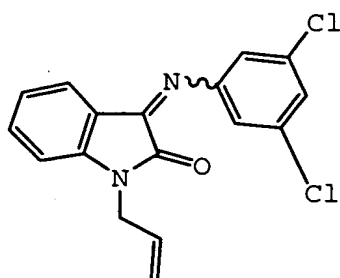


136. The method of claim 130, wherein A is A' and A' is

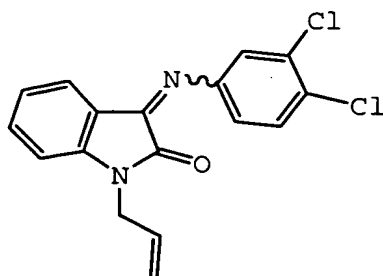


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137. The method of claim 136, wherein the compound is:



; or



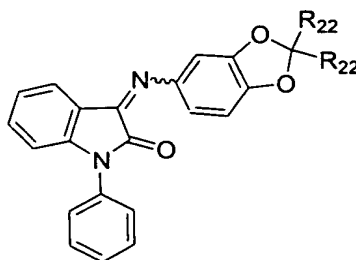
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138. The method of claim 121, wherein B is Q<sub>6</sub>.

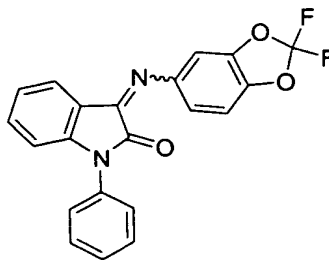
5 139. The method of claim 138, wherein A is aryl.

140. The method of claim 139, wherein the compound has the structure:

10



15 141. The method of claim 140, wherein the compound is:



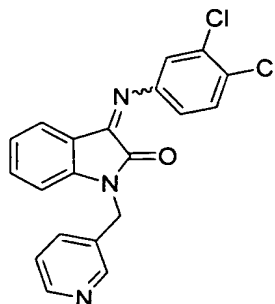
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142. The method of claim 122, wherein B is aryl.

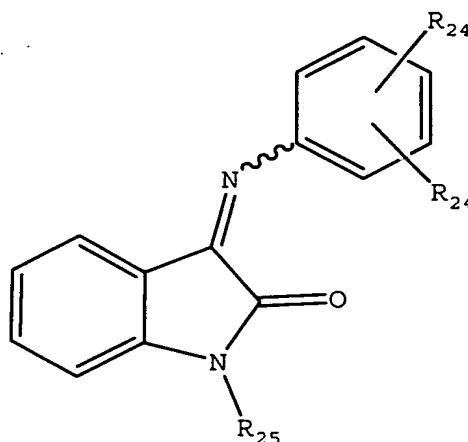
143. The method of claim 142, wherein A is  $(\text{CHR}_{17})_n - (\text{CHR}_{17})_n - \text{Z}$ .

144. The method of claim 143, wherein the compound is:

5



10 145. The method of claim 119, wherein the compound has the structure:



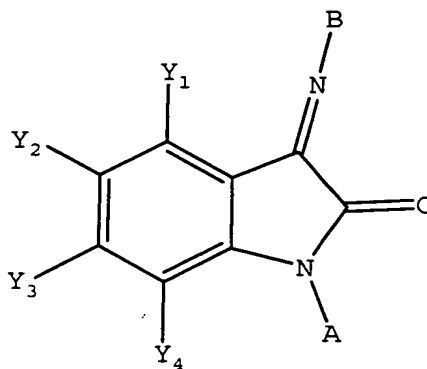
15 wherein each  $\text{R}_{24}$  is independently one or more of the following: H, F, Cl, Br, I,  $\text{CF}_3$ ,  $\text{OCH}_3$  or  $\text{NO}_2$ ; and

wherein  $R_{25}$  is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br,  $CF_3$ ,  $NO_2$ .

5

146. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

10



wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
15 monofluoroalkyl or polyfluoroalkyl; straight chained  
or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
20 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
carbon atoms can constitute a methylenedioxy group;

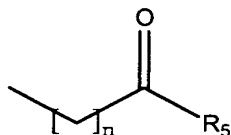
wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or

polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  $C_5-C_7$  cycloalkenyl, aryl or aryl( $C_1-C_6$ )alkyl;

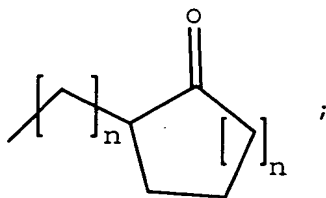
5 wherein A is A',  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or branched  $C_1-C_7$  alkyl, aryl, heteroaryl, aryl( $C_1-C_6$ )alkyl, heteroaryl( $C_1-C_6$ )alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or  $(CHR_{17})-(CHR_{17})_n-Z$ ;

10

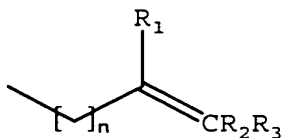
wherein A' is



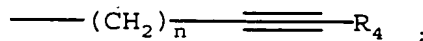
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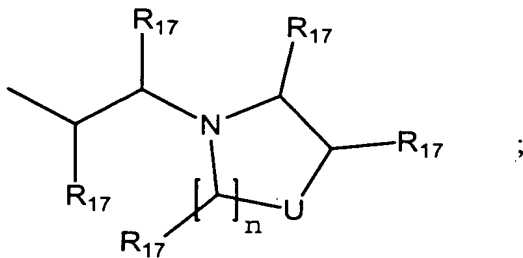
; or



;

15

wherein  $Q_3$  is



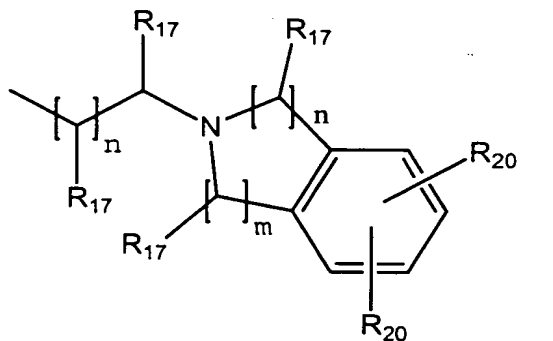
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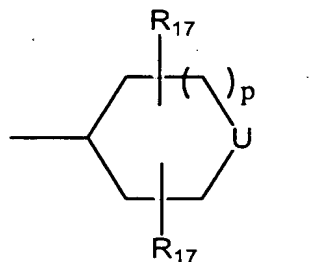


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wherein  $Q_4$  is



wherein  $Q_5$  is



10

wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

15

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, - $OR_6$ , aryl or heteroaryl;

20

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl, - $N(R_4)_2$ , - $OR_6$  or aryl;

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

5 wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

15 wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25 wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein each  $m$  is an integer from 0 to 4 inclusive;

30

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each  $p$  is an integer from 0 to 2 inclusive;

wherein  $U$  is  $O$ ,  $-NR_{16}$ ,  $S$ ,  $C(R_{17})_2$ , or  $-NSO_2R_{15}$ ;

5 wherein  $Z$  is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

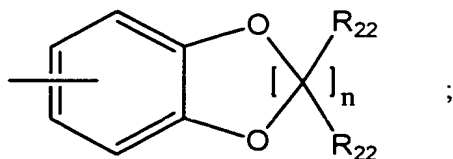
15 wherein  $q$  is an integer from 2 to 4 inclusive;

wherein  $B$  is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ;

20 provided however, if  $B$  is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CN$ , methyl, ethyl or methoxy;

25 wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

30 wherein  $Q_6$  is



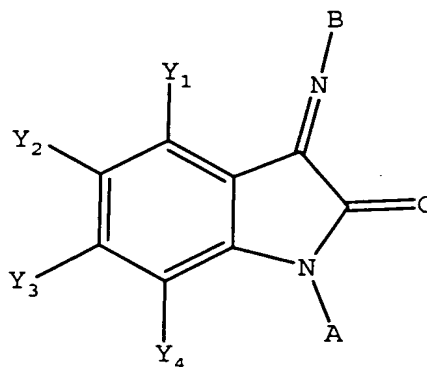
wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1-C_4$  alkyl;

5

or a pharmaceutically acceptable salt thereof.

147. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

10



- wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently - H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, or  $C_5-C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent

20

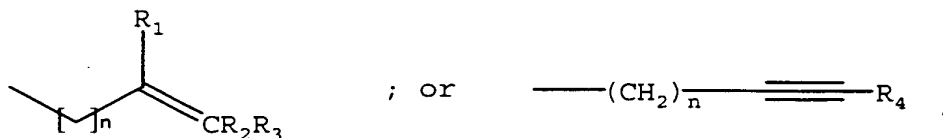
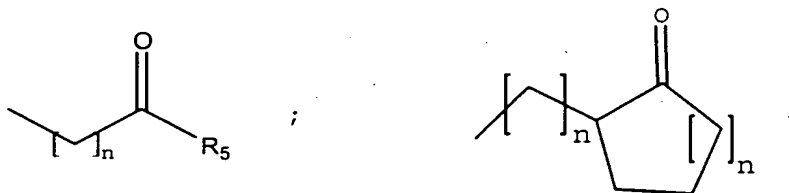
carbon atoms can constitute a methylenedioxy group;

wherein each  $R_i$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
5 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
10 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is

15



20

wherein  $R_1$  and  $R_2$  are each independently H, straight  
chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
 $\text{NO}_2$ , or -CN;

25

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
alkyl, -F, -Cl, -Br, -I, - $\text{NO}_2$ , -CN, -OR<sub>6</sub> aryl or

heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $-N(R_4)_2$ ,  $-OR_6$  or aryl;

5

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

10

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

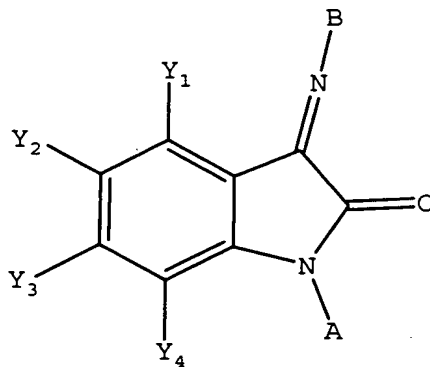
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wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

20 148. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

25

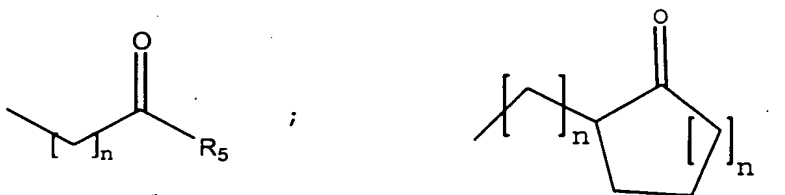


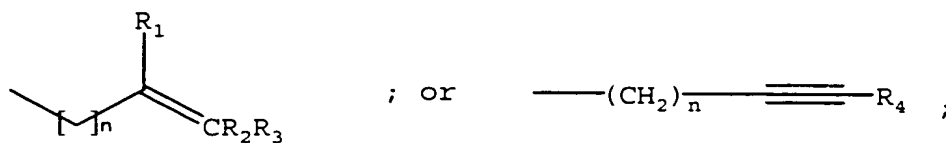
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 5 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 10 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 15 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 20 heteroaryl( $C_1$ - $C_6$ )alkyl;

wherein A' is

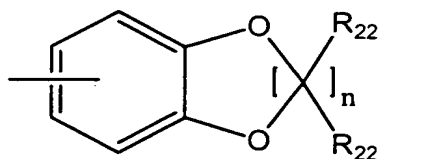




5 wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is  
10 heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is



15

wherein n is an integer from 1 to 4 inclusive;

wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

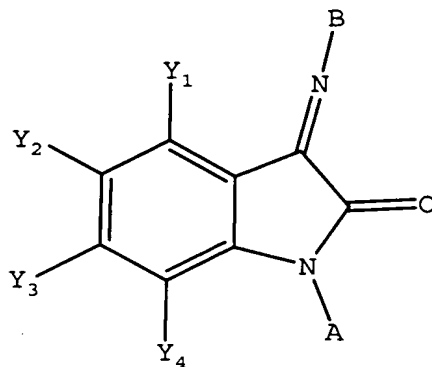
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or a pharmaceutically acceptable salt thereof.

25 149. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the



subject's anxiety wherein the compound has the structure:

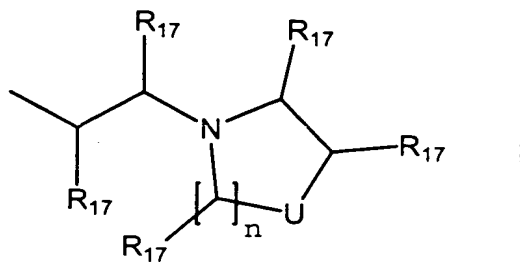


5 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained  
or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
10 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
carbon atoms can constitute a methylenedioxy group;

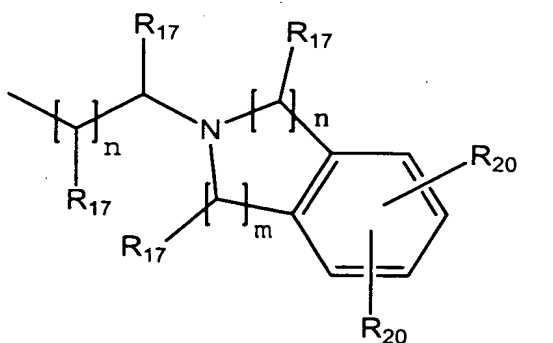
15 wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

20 wherein A is  $Q_3$ ,  $Q_4$ ,  $Q_5$ , aryl substituted with an  
aryl or heteroaryl, heteroaryl substituted with an  
aryl or heteroaryl, or  $(CHR_{17}) - (CHR_{17})_n - Z$ ;

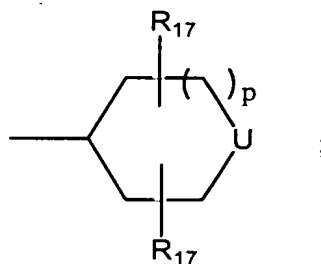
25 wherein  $Q_3$  is



wherein Q<sub>4</sub> is



5 wherein Q<sub>5</sub> is



10 wherein each R<sub>17</sub> is independently H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

15

wherein each R<sub>20</sub> is independently -H; straight

chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R<sub>21</sub> is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, -NR<sub>16</sub>, S, C(R<sub>17</sub>)<sub>2</sub>, or -NSO<sub>2</sub>R<sub>16</sub>;

wherein Z is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

wherein R<sub>16</sub> is straight chained or branched  $C_1$ - $C_7$

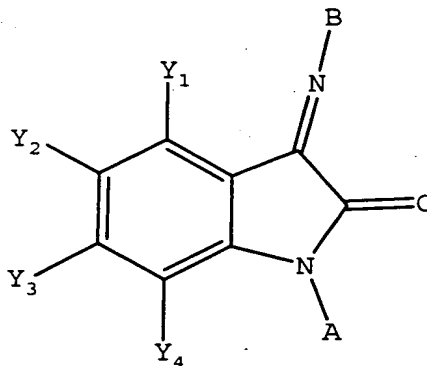
alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>  
polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl,  
5 C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>q</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

wherein B is aryl, or heteroaryl; provided however,  
if B is aryl or heteroaryl the carbon atom or carbon  
atoms ortho to the nitrogen atom of the imine bond  
10 may only be substituted with one or more of the  
following -F, -Cl, -Br, -I, -CN, methyl, ethyl or  
methoxy;

or a pharmaceutically acceptable salt thereof.  
15

150. The method of claim 146, 147, 148, or 149, wherein  
the compound is enantiomerically and  
diastereomerically pure.  
20
151. The method of claim 146, 147, 148, or 149, wherein  
the compound is enantiomerically or  
diastereomerically pure compound.
- 25 152. The method of claim 146, 147, 148, or 149, wherein  
the compound is a pure Z imine isomer or a pure Z  
alkene isomer.
- 30 153. The method of claim 146, 147, 148, or 149, wherein  
the compound is a pure E imine isomer or a pure E  
alkene isomer.

154. The method of claim 146 or 147, wherein the compound has the structure:

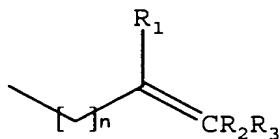


wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -  
10 F,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

15 wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$   
alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
heteroaryl( $C_1$ - $C_6$ )alkyl; and

wherein  $A'$  is



155. The method of claim 146 or 147, wherein B is heteroaryl.

156. The method of claim 146 or 147, wherein B is aryl.

5

157. The method of claim 156, wherein B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>,  
10 -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

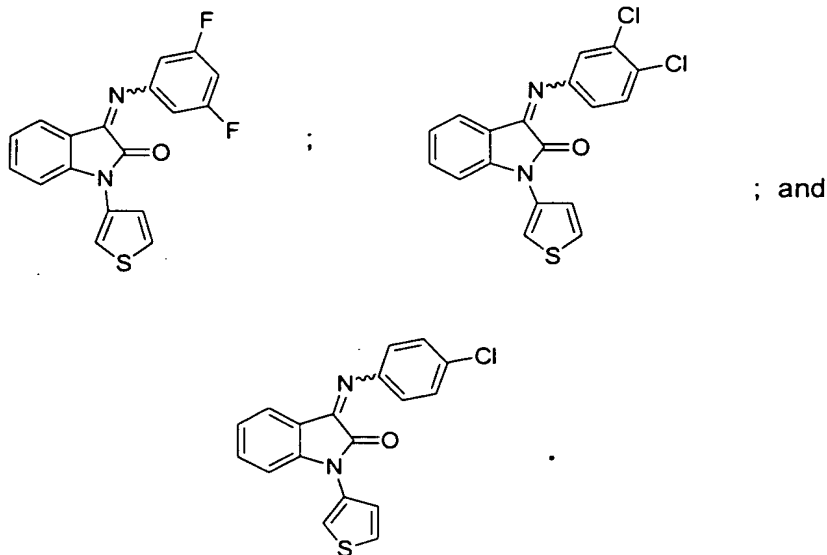
158. The method of claim 157, wherein A is aryl.

159. The method of claim 157, wherein A is heteroaryl.

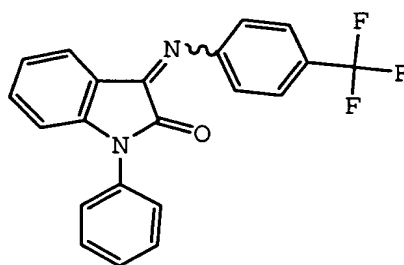
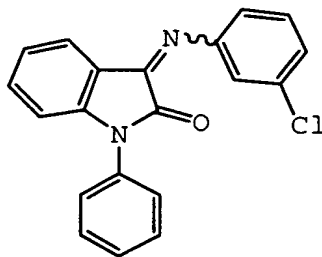
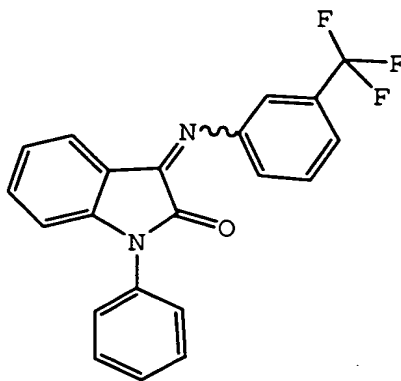
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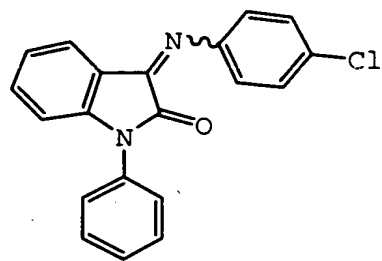
160. The method of claim 159, wherein the compound is selected from the group consisting of:

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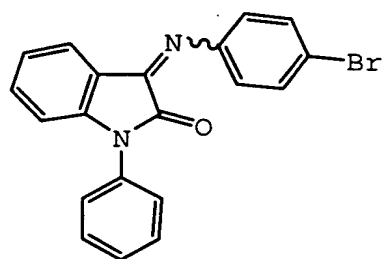


161. The method of claim 158, wherein the compound is selected from the group consisting of:

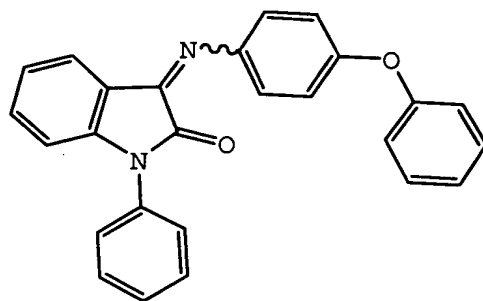




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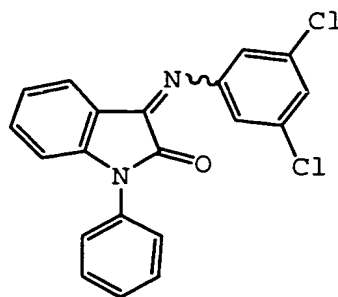


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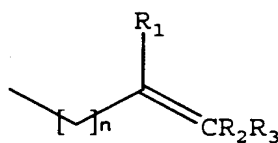


; and





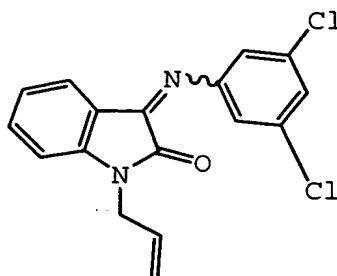
162. The method of claim 156, wherein A is A', and A' is



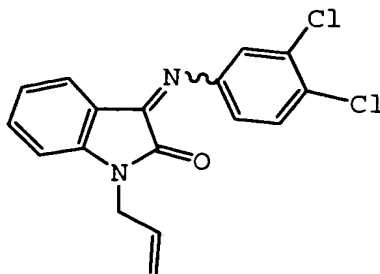
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163. The method of claim 162, wherein the compound is:

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; or

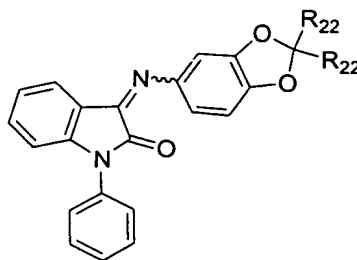


164. The method of claim 148, wherein B is Q<sub>6</sub>.

5 165. The method of claim 164, wherein A is aryl.

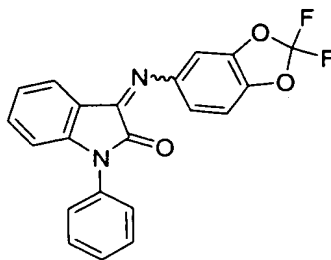
166. The method of claim 165, wherein the compound has the structure:

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167. The method of claim 166, wherein the compound is:

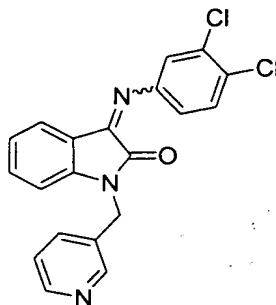


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168. The method of claim 149, wherein B is aryl.

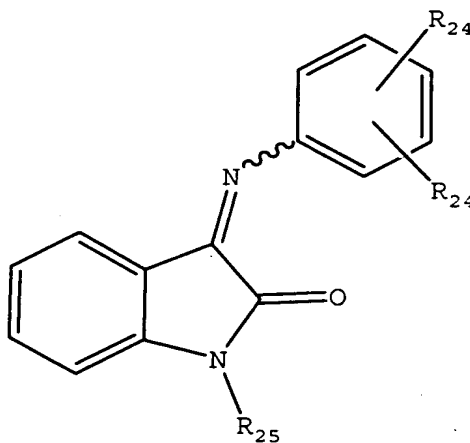
169. The method of claim 168, wherein A is  $(\text{CHR}_{17})-(\text{CHR}_{17})_n-\text{Z}$ .

170. The method of claim 169, wherein the compound is:



5

171. The method of claim 146, wherein the compound has the structure:



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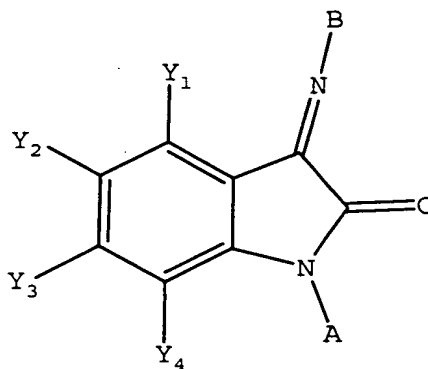
wherein each  $\text{R}_{24}$  is independently one or more of the following: H, F, Cl, Br, I,  $\text{CF}_3$ ,  $\text{OCH}_3$  or  $\text{NO}_2$ ; and

wherein  $R_{25}$  is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br,  $CF_3$ ,  $NO_2$ .

5

172. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

10



wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

20

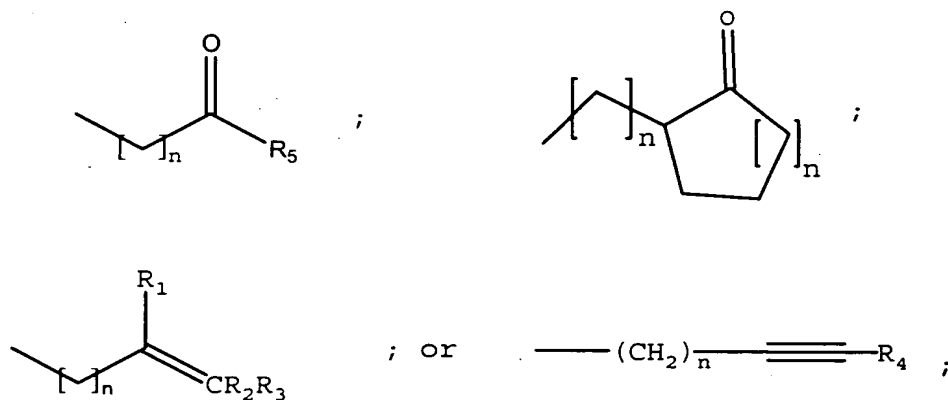
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or

polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, aryl or aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl;

5 wherein A is A', Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR<sub>17</sub>)-(CHR<sub>17</sub>)<sub>n</sub>-Z;

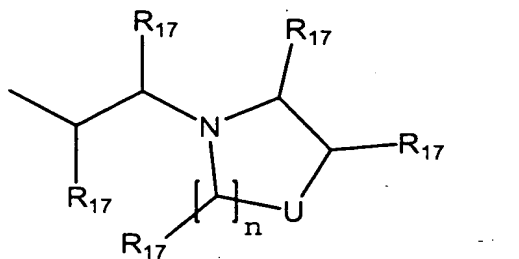
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wherein A' is



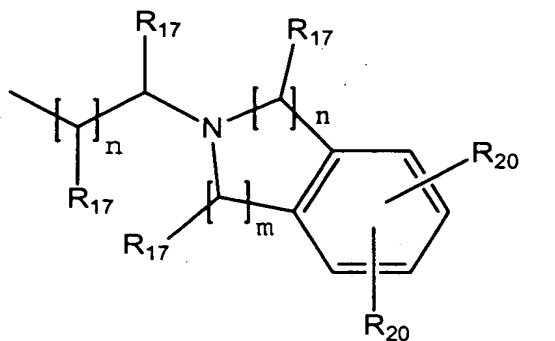
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wherein Q<sub>3</sub> is



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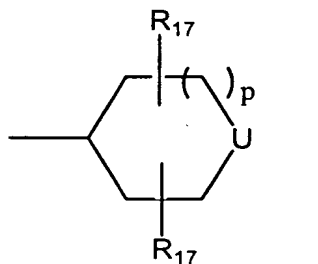
wherein  $Q_4$  is



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wherein  $Q_5$  is



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wherein  $R_1$  and  $R_2$  are each independently H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , or -CN;

20

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, - $NO_2$ , -CN, -OR<sub>6</sub>, aryl or heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $-N(R_4)_2$ ,  $-OR_6$  or aryl;

5 wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  
10  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

15 wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; -  
20  $OR_{21}$ ,  $-OCOR_{21}$ ,  $-COR_{21}$ ,  $-NCOR_{21}$ ,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or  $-COOR_{21}$ ; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25 wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

30

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

wherein each  $p$  is an integer from 0 to 2 inclusive;

5 wherein  $U$  is  $O$ ,  $-NR_{16}$ ,  $S$ ,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein  $Z$  is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

10 wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  
15  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

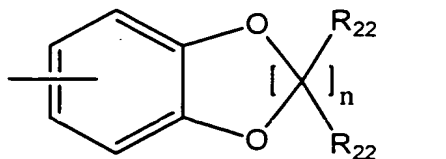
wherein  $q$  is an integer from 2 to 4 inclusive;

wherein  $B$  is aryl, heteroaryl, aryl substituted with  
20 an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ;  
provided however, if  $B$  is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with  
25 one or more of the following  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CN$ , methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the  
30 rings is heteroaryl; carbazole; or acridine;

wherein  $Q_6$  is





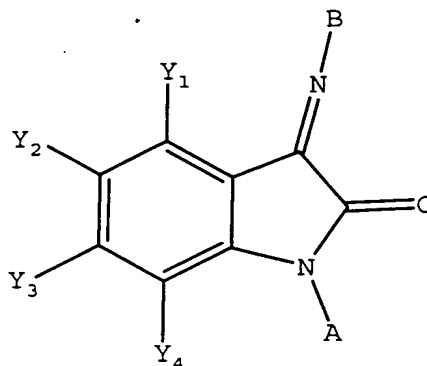
wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

5

or a pharmaceutically acceptable salt thereof.

173. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

10



wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 N( $R_4$ )<sub>2</sub>, -CON( $R_4$ )<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

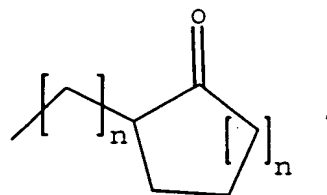
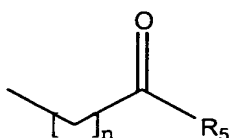
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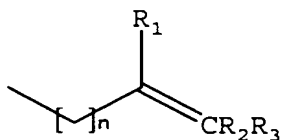
wherein each  $R_4$  is independently -H; straight chained  
or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
5 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is A', straight chained or branched  $C_1$ - $C_7$   
alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
10 heteroaryl( $C_1$ - $C_6$ )alkyl;

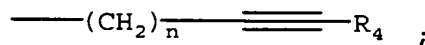
wherein A' is



15



; or



20 wherein  $R_1$  and  $R_2$  are each independently H, straight  
chained or branched  $C_1$ - $C_7$  alkyl, -F, -Cl, -Br, -I, -  
NO<sub>2</sub>, or -CN;

wherein  $R_3$  is H, straight chained or branched  $C_1$ - $C_7$   
25 alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub> aryl or

heteroaryl;

wherein  $R_5$  is straight chained or branched  $C_1$ - $C_7$  alkyl,  $-N(R_4)_2$ ,  $-OR_6$  or aryl;

5

wherein  $R_6$  is straight chained or branched  $C_1$ - $C_7$  alkyl or aryl;

10

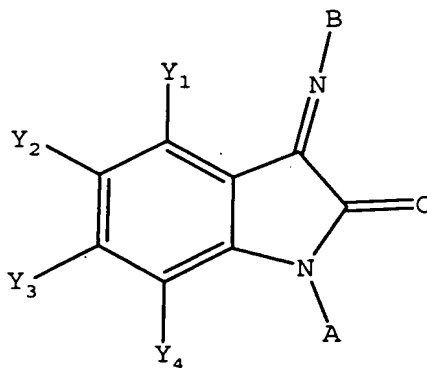
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

15

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

20 174. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



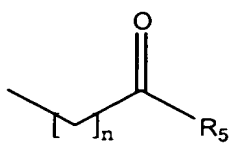
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wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 5 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -SR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -  
 N(R<sub>4</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; aryl or heteroaryl; or  
 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

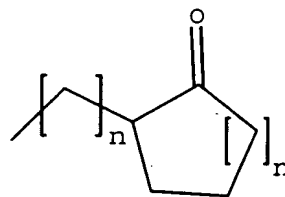
10 wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 15 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

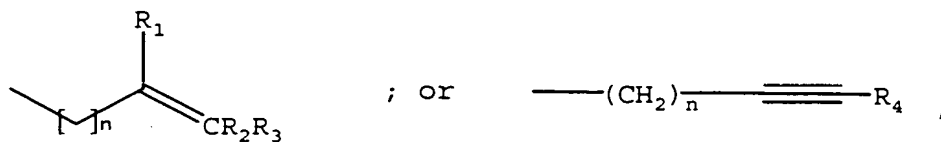
wherein A is A', straight chained or branched  $C_1$ - $C_7$   
 alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or  
 heteroaryl( $C_1$ - $C_6$ )alkyl;

20 wherein A' is



;





5

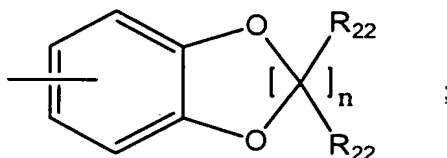
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

10

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

15

wherein Q<sub>6</sub> is



20

wherein n is an integer from 1 to 4 inclusive;

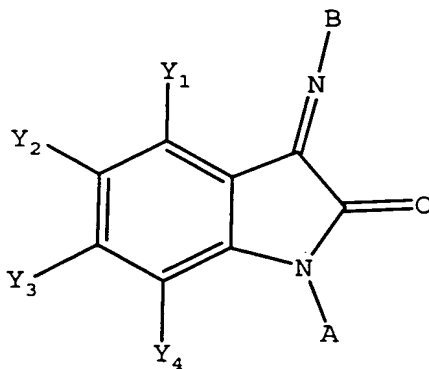
wherein each R<sub>22</sub> is independently H, F, Cl, or straight chained or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

25

or a pharmaceutically acceptable salt thereof.

175. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

5



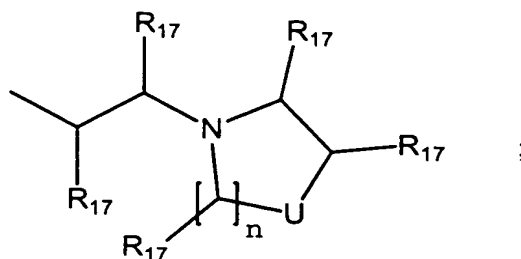
wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 10 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or  
 15 any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent  
 carbon atoms can constitute a methylenedioxy group;

wherein each  $R_4$  is independently -H; straight chained  
 or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or  
 20 polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$   
 alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$   
 cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $Q_3$ ,  $Q_4$ ,  $Q_5$ , aryl substituted with an  
 25 aryl or heteroaryl, heteroaryl substituted with an

aryl or heteroaryl, or  $(\text{CHR}_{17})_n - \text{Z}$ ;

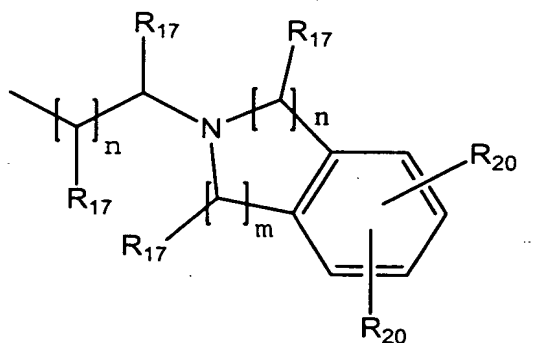
wherein  $Q_3$  is



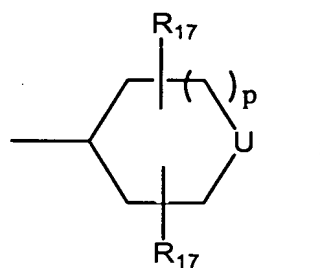
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10

wherein  $Q_4$  is



wherein  $Q_5$  is



15

wherein each  $R_{17}$  is independently H; straight chained

or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein  $q$  is an integer from 2 to 4 inclusive;

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;



wherein each p is an integer from 0 to 2 inclusive;

wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

5 wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

15 wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

25 176. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is an enantiomerically and diastereomerically pure compound.

30 177. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is an enantiomerically or diastereomerically pure compound.

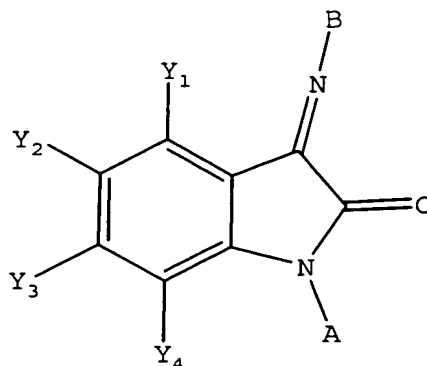
178. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is a pure Z imine isomer or a pure Z alkene isomer.

5 179. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the compound is a pure E imine isomer or a pure E alkene isomer.

10 180. The pharmaceutical composition of claim 172, 173, 174, or 175, wherein the composition can be administered orally.

181. The pharmaceutical composition of claim 172 or 173, wherein the compound has the structure:

15



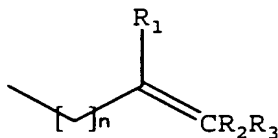
20 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl;  $-CF_3$ , -F, -Cl, -Br, -I,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

25 wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$

alkyl, aryl, heteroaryl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl; and

wherein A' is



5

182. The pharmaceutical composition of claim 172, 173 or 175, wherein B is heteroaryl.

10 183. The pharmaceutical composition of claim 172 or 173, wherein B is aryl.

184. The pharmaceutical composition of claim 183, wherein B is phenyl and the phenyl is optionally substituted  
15 with one or more of the following: -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

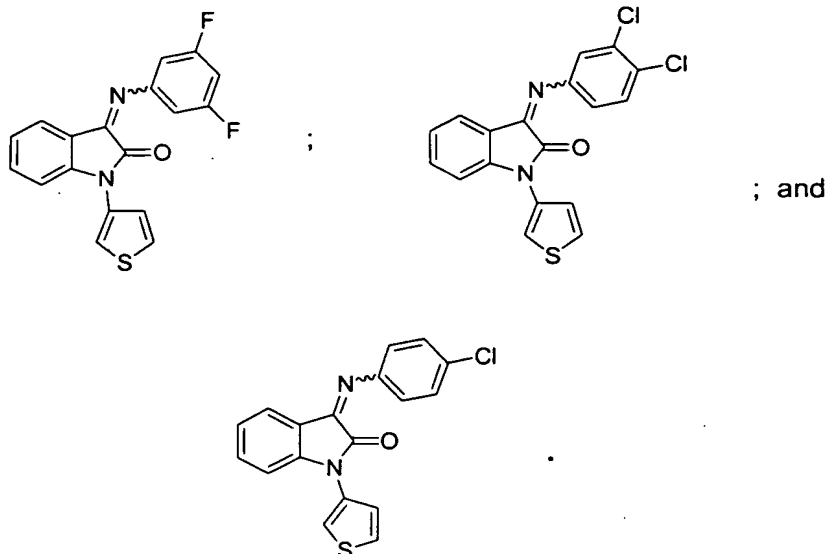
185. The pharmaceutical composition of claim 184, wherein  
20 A is aryl.

186. The pharmaceutical composition of claim 184, wherein A is heteroaryl.

25

187. The pharmaceutical composition of claim 186, wherein the compound is selected from the group consisting of:

5



188. The pharmaceutical composition of claim 174, wherein  
10 B is Q<sub>6</sub>.

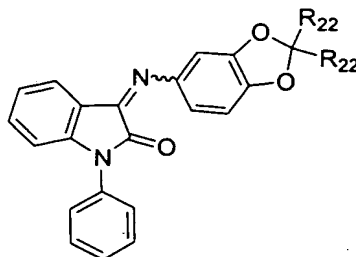
189. The pharmaceutical composition of claim 188, wherein  
A is aryl.

15

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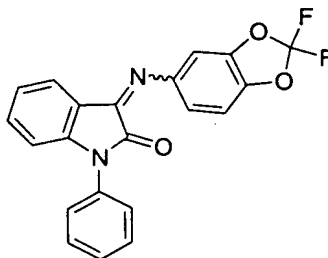
190. The pharmaceutical composition of claim 189, wherein the compound has the structure:

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191. The pharmaceutical composition of claim 190, wherein the compound is:



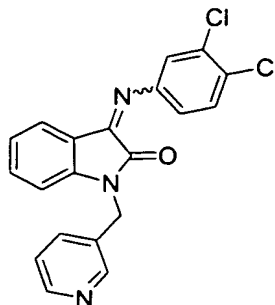
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192. The pharmaceutical composition of claim 175, wherein B is aryl.

20

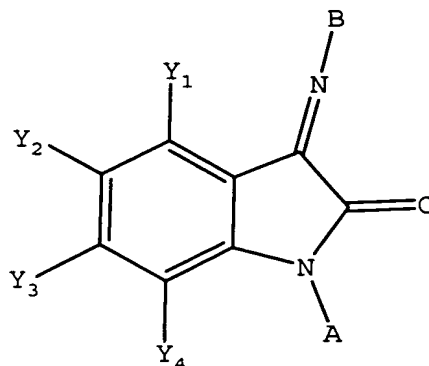
193. The pharmaceutical composition of claim 192, wherein A is  $(\text{CHR}_{17}) - (\text{CHR}_{17})_n - \text{Z}$ .

194. The pharmaceutical composition of claim 193, wherein the compound is:



5

195. A compound having the structure:



10

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -  
 I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , -  
 $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or

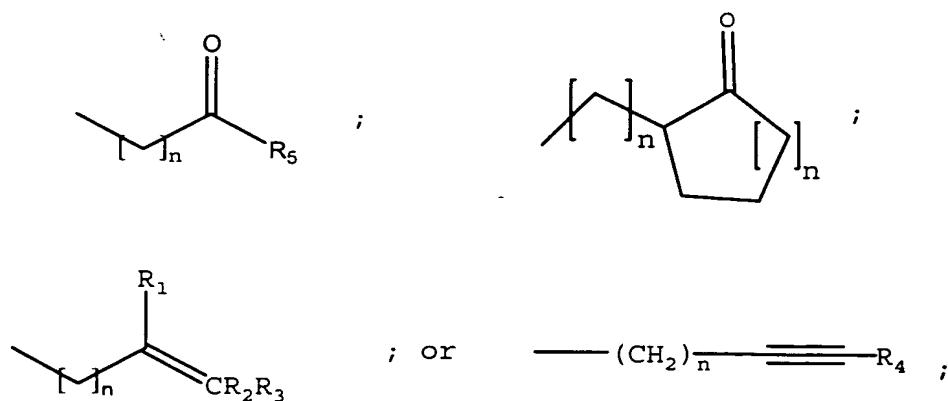
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any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

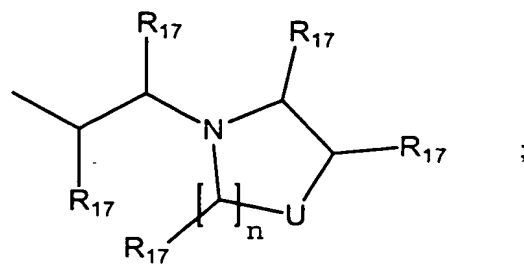
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

wherein A is  $A'$ ,  $Q_3$ ,  $Q_4$ ,  $Q_5$ , straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl, heteroaryl( $C_1$ - $C_6$ )alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or  $(CHR_{17})-(CHR_{17})_n-Z$ ;

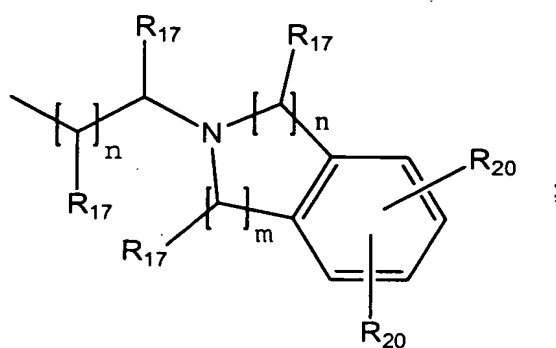
wherein  $A'$  is



wherein  $Q_3$  is

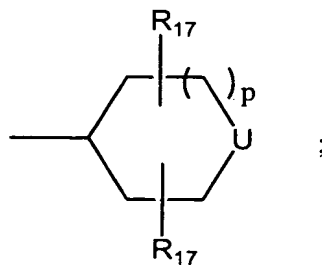


5            wherein Q<sub>4</sub> is



10

wherein Q<sub>5</sub> is



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wherein R<sub>1</sub> and R<sub>2</sub> are each independently H, straight



chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, or -CN;

5 wherein R<sub>3</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub>, aryl or heteroaryl;

10 wherein R<sub>5</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>6</sub> or aryl;

wherein R<sub>6</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl or aryl;

15 wherein each R<sub>17</sub> is independently H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, -(CH<sub>2</sub>)<sub>m</sub>-Z, or (CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-CH<sub>3</sub>;

20

25 wherein each R<sub>20</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>5</sub>-C<sub>7</sub> cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>, -N(R<sub>21</sub>)<sub>2</sub>, -CON(R<sub>21</sub>)<sub>2</sub>, or -COOR<sub>21</sub>; aryl or heteroaryl; or two R<sub>20</sub> groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

30

wherein each R<sub>21</sub> is independently -H; straight

chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

5

wherein each  $m$  is an integer from 0 to 4 inclusive;

wherein each  $n$  is an integer from 1 to 4 inclusive;

10

wherein each  $p$  is an integer from 0 to 2 inclusive;

wherein  $U$  is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

15

wherein  $Z$  is  $C_3$ - $C_{10}$  cycloalkyl,  $C_4$ - $C_7$  cyclic ether,  $C_4$ - $C_7$  cyclic thioether, aryl, or heteroaryl;

20

wherein  $R_{16}$  is straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

25

wherein  $q$  is an integer from 2 to 4 inclusive;

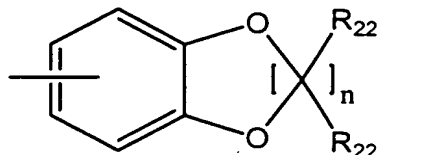
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wherein  $B$  is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or  $Q_6$ ; provided however, if  $B$  is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CN$ ,

methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the  
 5 rings is heteroaryl; carbazole; or acridine;

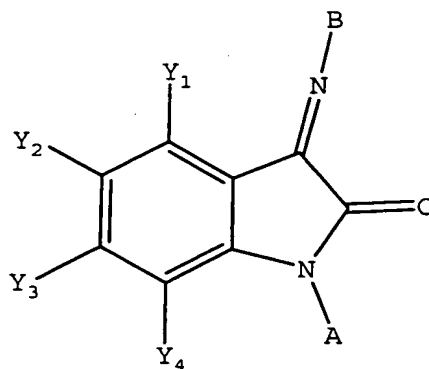
wherein  $Q_6$  is



10 wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

or a pharmaceutically acceptable salt thereof.

15 196. A compound having the structure:



wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -  
 H; straight chained or branched  $C_1$ - $C_7$  alkyl,  
 20 monofluoroalkyl or polyfluoroalkyl; straight chained  
 or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$   
 cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -

I;  $-\text{NO}_2$ ;  $-\text{N}_3$ ;  $-\text{CN}$ ;  $-\text{OR}_4$ ,  $-\text{SR}_4$ ,  $-\text{OCOR}_4$ ,  $-\text{COR}_4$ ,  $-\text{NCOR}_4$ ,  $-\text{N}(\text{R}_4)_2$ ,  $-\text{CON}(\text{R}_4)_2$ , or  $-\text{COOR}_4$ ; aryl or heteroaryl; or any two of  $\text{Y}_1$ ,  $\text{Y}_2$ ,  $\text{Y}_3$  and  $\text{Y}_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

5

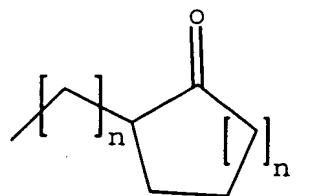
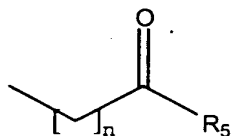
wherein each  $\text{R}_4$  is independently  $-\text{H}$ ; straight chained or branched  $\text{C}_1$ - $\text{C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $\text{C}_2$ - $\text{C}_7$  alkenyl or alkynyl;  $\text{C}_3$ - $\text{C}_7$  cycloalkyl,  $\text{C}_5$ - $\text{C}_7$  cycloalkenyl, aryl or aryl( $\text{C}_1$ - $\text{C}_6$ )alkyl;

10

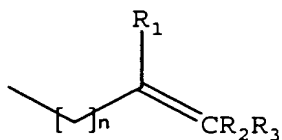
wherein A is A', straight chained or branched  $\text{C}_1$ - $\text{C}_7$  alkyl, aryl, heteroaryl, aryl( $\text{C}_1$ - $\text{C}_6$ )alkyl or heteroaryl( $\text{C}_1$ - $\text{C}_6$ )alkyl;

15

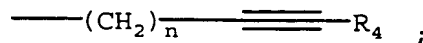
wherein A' is



20



; or



25

wherein  $\text{R}_1$  and  $\text{R}_2$  are each independently H, straight chained or branched  $\text{C}_1$ - $\text{C}_7$  alkyl,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ , -

NO<sub>2</sub>, or -CN;

5 wherein R<sub>3</sub> is H, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>6</sub> aryl or heteroaryl;

wherein R<sub>5</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>6</sub> or aryl;

10 wherein R<sub>6</sub> is straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl or aryl;

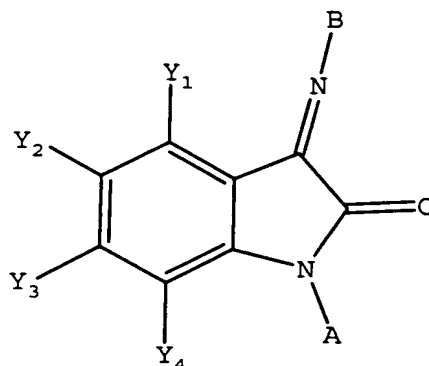
15 wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

20 wherein n is an integer from 1 to 4 inclusive;

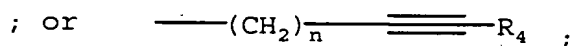
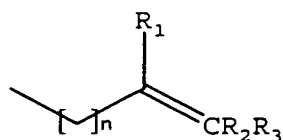
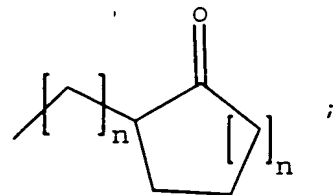
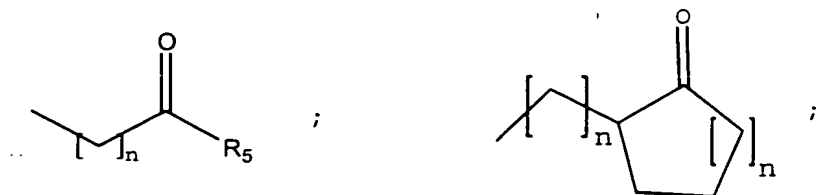
or a pharmaceutically acceptable salt thereof.

25

197. A compound having the structure:



5. wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;
- 10
- 15 wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;
- 20
- wherein A is A', straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl;
- 25 wherein A' is

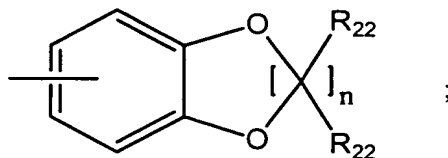


5

wherein B is aryl substituted with an aryl or  
 10 heteroaryl, heteroaryl substituted with an aryl or  
 heteroaryl, tricyclic heteroaryl or Q<sub>6</sub>;

wherein a tricyclic heteroaryl is a fused three ring  
 aromatic system in which one or more of the rings is  
 15 heteroaryl; carbazole; or acridine;

wherein Q<sub>6</sub> is



20

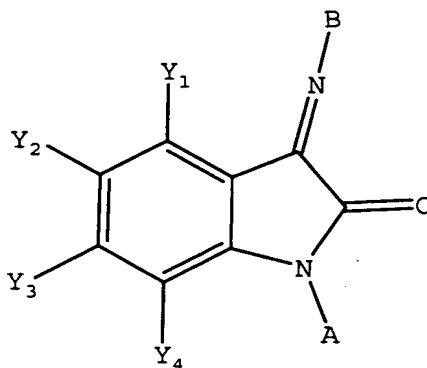
wherein n is an integer from 1 to 4 inclusive;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

or a pharmaceutically acceptable salt thereof.

5

198. A compound having the structure:



10

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $SR_4$ , - $OCOR_4$ , - $COR_4$ , - $NCOR_4$ , - $N(R_4)_2$ , - $CON(R_4)_2$ , or - $COOR_4$ ; aryl or heteroaryl; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  present on adjacent carbon atoms can constitute a methylenedioxy group;

20

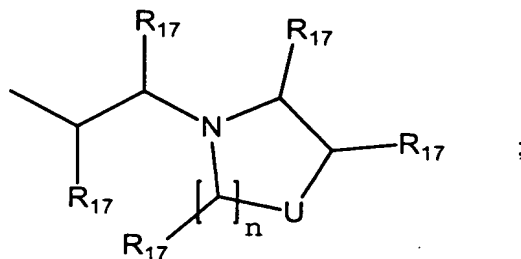
wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl, aryl or aryl( $C_1$ - $C_6$ )alkyl;

25



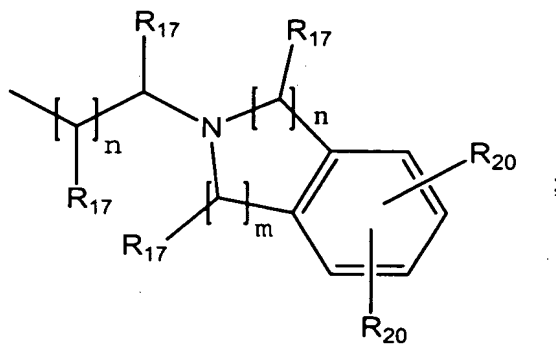
wherein A is Q<sub>3</sub>, Q<sub>4</sub>, Q<sub>5</sub>, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR<sub>17</sub>) - (CHR<sub>17</sub>)<sub>n</sub>-Z;

5 wherein Q<sub>3</sub> is

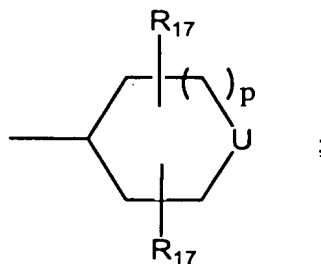


10

wherein Q<sub>4</sub> is



15 wherein Q<sub>5</sub> is



wherein each  $R_{17}$  is independently H; straight chained or branched  $C_1$ - $C_7$  alkyl, straight chained or branched  $C_1$ - $C_7$  monofluoroalkyl, straight chained or branched  $C_1$ - $C_7$  polyfluoroalkyl, straight chained or branched  $C_2$ - $C_7$  alkenyl, straight chained or branched  $C_2$ - $C_7$  alkynyl,  $C_5$ - $C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_n-O-(CH_2)_m-CH_3$ ;

wherein each  $R_{20}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl or  $C_5$ - $C_7$  cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN; -OR<sub>21</sub>, -OCOR<sub>21</sub>, -COR<sub>21</sub>, -NCOR<sub>21</sub>,  $-N(R_{21})_2$ ,  $-CON(R_{21})_2$ , or -COOR<sub>21</sub>; aryl or heteroaryl; or two  $R_{20}$  groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each  $R_{21}$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl,  $C_5$ - $C_7$  cycloalkenyl or aryl;

wherein each  $R_{22}$  is independently H, F, Cl, or straight chained or branched  $C_1$ - $C_4$  alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

5 wherein U is O,  $-NR_{16}$ , S,  $C(R_{17})_2$ , or  $-NSO_2R_{16}$ ;

wherein Z is  $C_3-C_{10}$  cycloalkyl,  $C_4-C_7$  cyclic ether,  $C_4-C_7$  cyclic thioether, aryl, or heteroaryl;

10 wherein  $R_{16}$  is straight chained or branched  $C_1-C_7$  alkyl, straight chained or branched  $C_1-C_7$  monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  
15  $C_5-C_7$  cycloalkenyl,  $-(CH_2)_m-Z$ , or  $(CH_2)_q-O-(CH_2)_m-CH_3$ ;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond  
20 may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

25 or a pharmaceutically acceptable salt thereof.

199. An enantiomerically and diastereomerically pure compound of claim 195, 196, 197, or 198.

30 200. An enantiomerically or diastereomerically pure compound of claim 195, 196, 197, or 198.

201. A pure Z imine isomer or a pure Z alkene isomer of

the compound of claim 195, 196, 197, or 198.

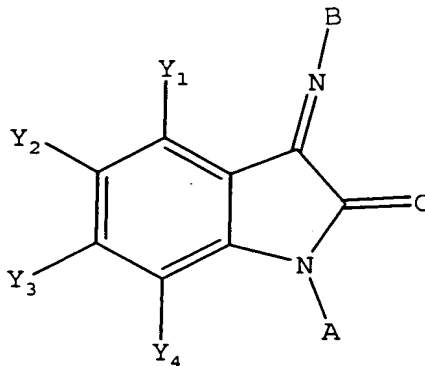
202. A pure E imine isomer or a pure E alkene isomer of the compound of claim 195, 196, 197, or 198.

5

203. The compound of claim 195, 196, 197, or 198, wherein the compound can be administered orally.

10

204. The compound of claim 195 or 196, wherein the compound has the structure:



15

wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ , and  $Y_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , -F, -Cl, -Br, -I,  $-OR_4$ ,  $-N(R_4)_2$ , or  $-CON(R_4)_2$ ;

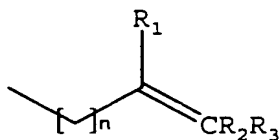
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wherein each  $R_4$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl,  $-CF_3$ , or phenyl;

wherein A is  $A'$ , straight chained or branched  $C_1$ - $C_7$  alkyl, aryl, heteroaryl, aryl( $C_1$ - $C_6$ )alkyl or heteroaryl( $C_1$ - $C_6$ )alkyl; and

25

wherein  $A'$  is



205. The compound of claim 195, 196 or 198, wherein B is heteroaryl.

5

206. The compound of claim 195 or 196, wherein B is aryl.

207. The compound of claim 206, wherein B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, -CF<sub>3</sub>, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -NCOR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>.

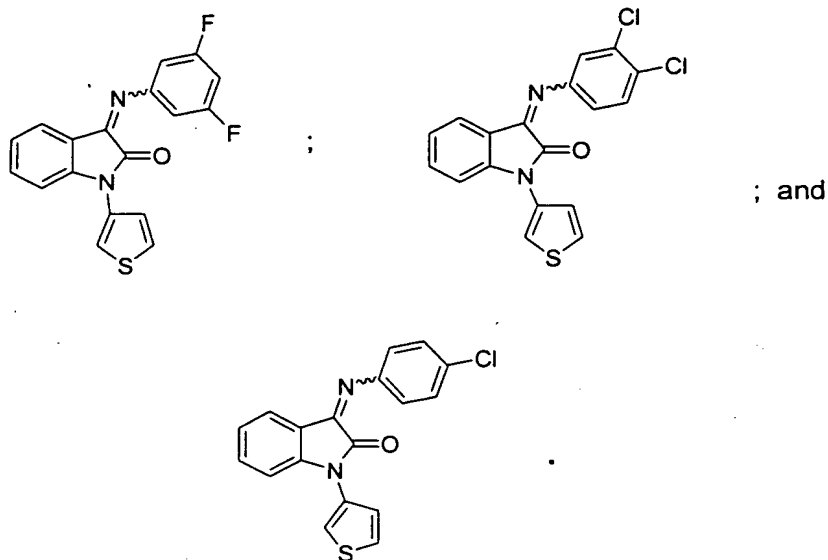
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208. The compound of claim 207, wherein A is aryl.

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209. The compound of claim 207, wherein A is heteroaryl.

210. The compound of claim 209, wherein the compound is selected from the group consisting of:

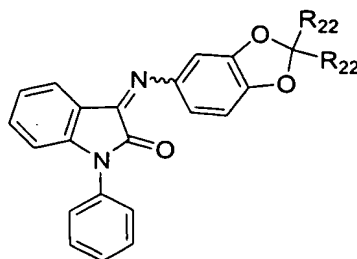


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211. The compound of claim 197, wherein B is Q<sub>6</sub>.

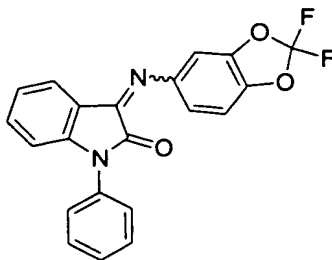
10 212. The compound of claim 211, wherein A is aryl.

213. The compound of claim 212, wherein the compound has the structure:



15

214. The compound of claim 213, wherein the compound is:

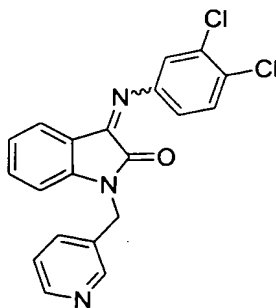


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215. The compound of claim 198, wherein B is aryl.

216. The compound of claim 215, wherein A is  $(\text{CHR}_{17}) -$   
 10  $(\text{CHR}_{17})_n - \text{Z}$ .

217. The compound of claim 215, wherein the compound is:



15

218. A pure Z imine isomer of the compound of claim 195,  
 196, 197 or 198.

219. A pure E imine isomer of the compound of claim 195,  
 20 196, 197 or 198.

220. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 195, 196, 197 or 198, and a pharmaceutically acceptable carrier.

5

221. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 195, 196, 197 or 198, and a pharmaceutically acceptable carrier.

10

222. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 195, 196, 197 or 198, and a pharmaceutically acceptable carrier.

15

223. A method of treating a subject suffering from depression which comprises administering to the subject an amount of the compound of claim 195, 196, 197 or 198 effective to treat the subject's depression.

20

224. A method of treating a subject suffering from anxiety which comprises administering to the subject an amount of the compound of claim 195, 196, 197 or 198 effective to treat the subject's anxiety.

25

225. A method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of the compound of claim 195, 196, 197 or 198 effective to treat the subject's depression and anxiety.

30



226. A method of treating depression in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

- (a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;
- (b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10 $\mu$ M; and  
(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10 $\mu$ M; and
- (c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

227. The method of claim 226, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

228. The method of claim 227, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

229. The method of claim 228, wherein the receptor

antagonist binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

5        230. The method of claim 229, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

10       231. The method of claim 226, wherein the receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

15       232. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the human 5HT<sub>1B</sub>,  
20       human 5HT<sub>1D</sub>, human 5HT<sub>1E</sub>, human 5HT<sub>1F</sub>, human 5HT<sub>2A</sub>, rat 5HT<sub>2C</sub>, human 5HT<sub>6</sub> and human 5HT<sub>7</sub> receptors.

233. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a  
25       binding affinity at least ten-fold higher than the binding affinity with which it binds to the human histamine H<sub>1</sub> receptor.

234. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a  
30       binding affinity at least ten-fold higher than the binding affinity with which it binds to the human dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> receptors.

235. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human  $\alpha_{1A}$  adrenoceptor,  
5 the human  $\alpha_{1B}$  adrenoceptor and the human  $\alpha_{1D}$  adrenoceptor.

236. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding  
10 affinity with which it binds to the human  $\alpha_{2A}$  adrenoceptor, the human  $\alpha_{2B}$  adrenoceptor and the human  $\alpha_{2C}$  adrenoceptor.

237. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a  
15 binding affinity less than ten-fold higher than the binding affinity with which it binds to the human 5HT<sub>4</sub> receptor.

238. The method of claim 226, wherein the receptor antagonist also binds to the human GAL3 receptor with a  
20 binding affinity less than ten-fold higher than the binding affinity with which it binds to the human 5HT<sub>1A</sub> receptor.

239. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central  
25 monoamine oxidase A greater than 30 percent.

240. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central  
monoamine oxidase B greater than 30 percent.

30

241. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central  
monoamine oxidase A greater than 15 percent.

242. The method of claim 226, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 15 percent.

5

243. A method of treating anxiety in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

10

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and

15

(b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

20

244. The method of claim 243, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

25

245. The method of claim 244, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

30

246. The method of claim 245, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the binding affinity

with which it binds to the human GAL1 receptor.

247. The method of claim 246, wherein the receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

248. The method of claim 243, wherein the receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

249. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the human 5HT<sub>1B</sub>, human 5HT<sub>1D</sub>, human 5HT<sub>1E</sub>, human 5HT<sub>1F</sub>, human 5HT<sub>2A</sub>, rat 5HT<sub>2C</sub>, human 5HT<sub>6</sub> and human 5HT<sub>7</sub> receptors.

250. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human histamine H<sub>1</sub> receptor.

251. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub> receptors.

252. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a

binding affinity at least ten-fold higher than the binding affinity with which it binds to the human  $\alpha_{1A}$  adrenoceptor, the human  $\alpha_{1B}$  adrenoceptor and the human  $\alpha_{1D}$  adrenoceptor.

5      253. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human  $\alpha_{2A}$  adrenoceptor, the human  $\alpha_{2B}$  adrenoceptor and the human  $\alpha_{2C}$  adrenoceptor.

10

254. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human 5HT<sub>4</sub> receptor.

15

255. The method of claim 243, wherein the receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human 5HT<sub>1A</sub> receptor.

**Use Of GAL3 Receptor Antagonists For The Treatment Of  
Depression And/Or Anxiety And Compounds Useful in Such  
Methods**

**5    Abstract Of The Disclosure**

This invention is directed to pyrimidine and indolone derivatives which are selective antagonists for the GAL3 receptor. The invention provides a pharmaceutical composition comprising a therapeutically effective amount  
10 of a compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a pharmaceutical composition made by combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This  
15 invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a method of treating a subject  
20 suffering from depression and/or anxiety which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's depression and/or anxiety. This invention also provides a method of treating depression and/or anxiety in a subject which  
25 comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist.

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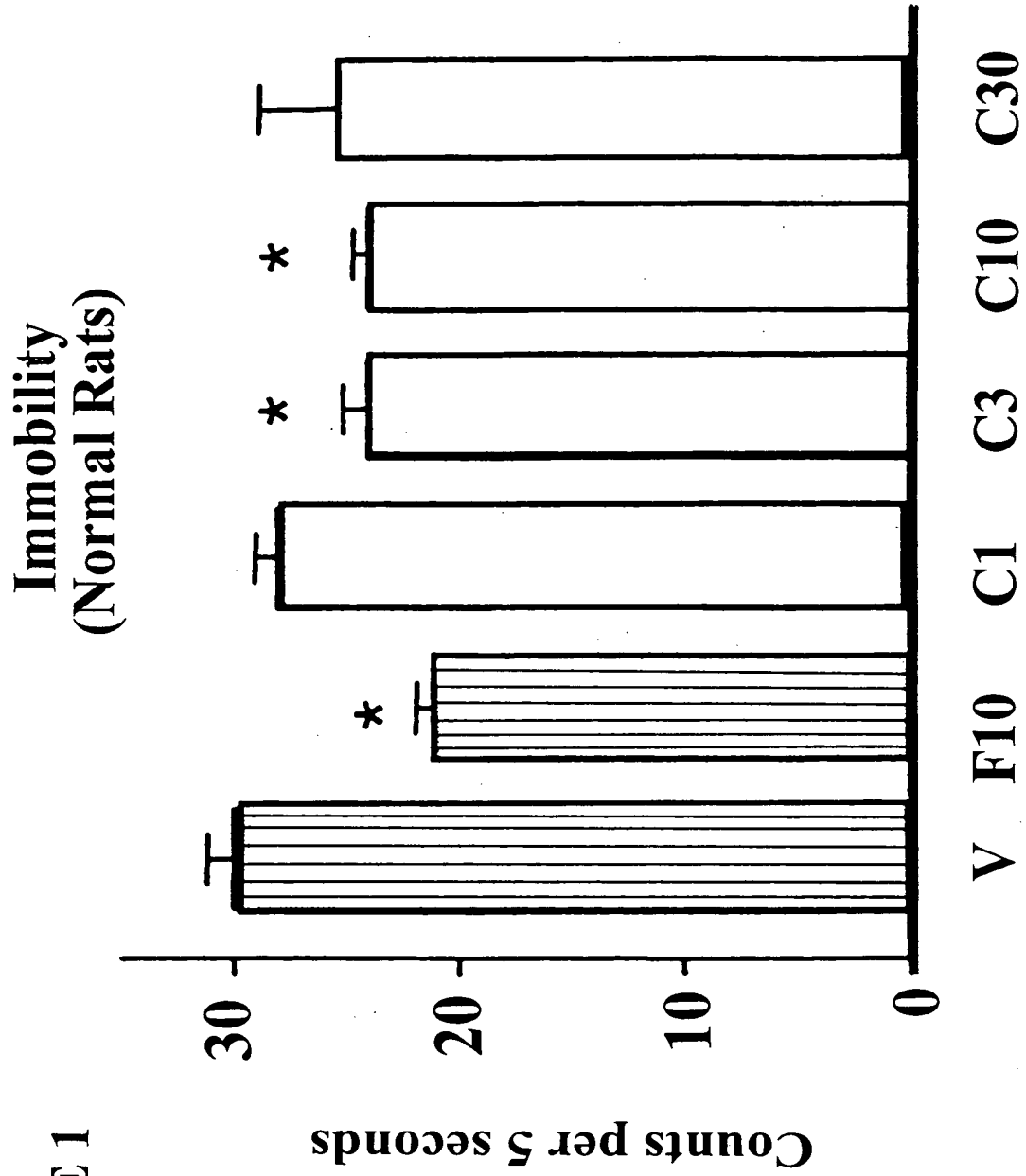
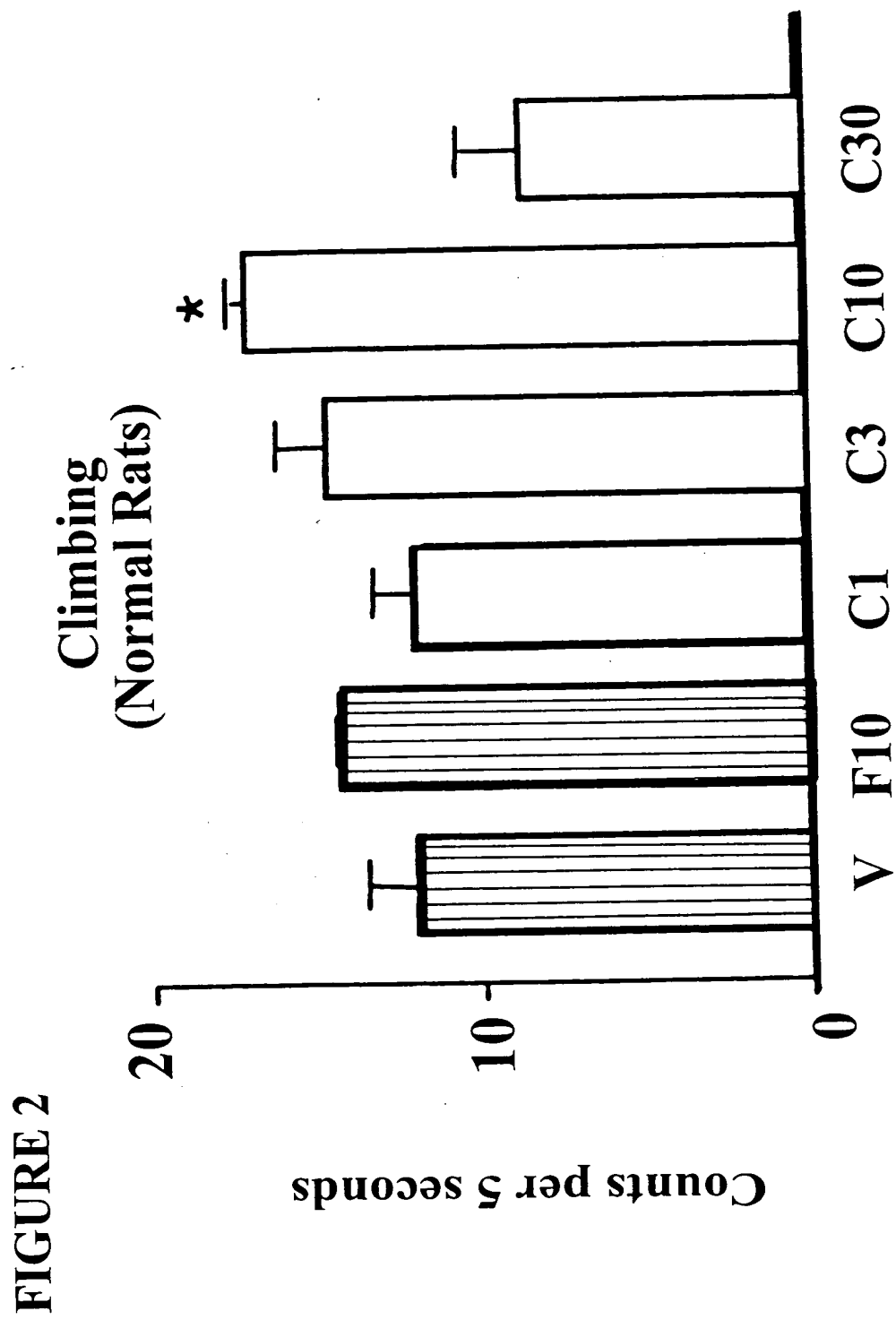


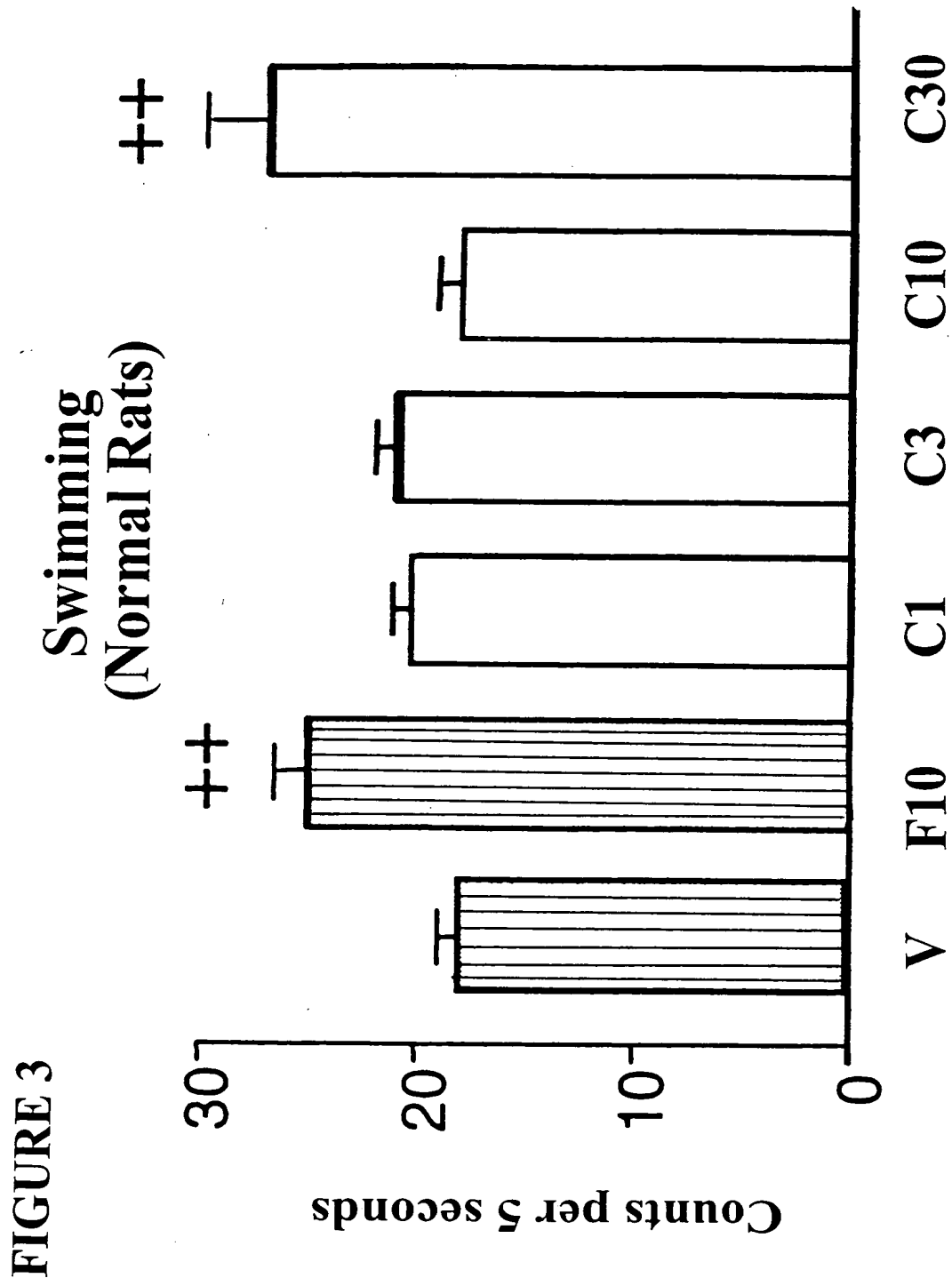
FIGURE 1



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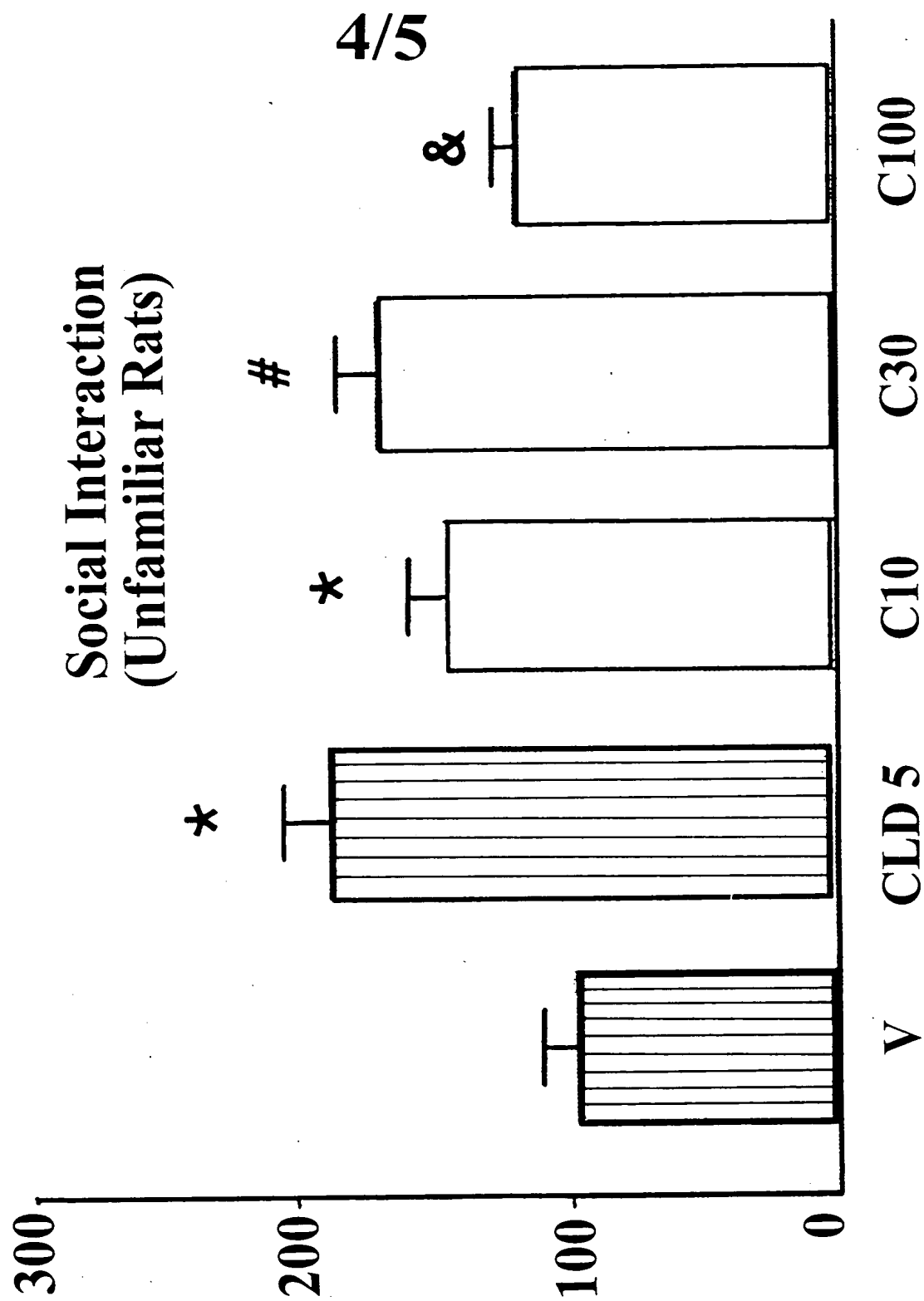


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**FIGURE 4**

Seconds of social interaction  $\pm$  S.E.M.



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FIGURE 5

